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**European Study on Medical, Industrial
and Research Applications of Nuclear
and Radiation Technology**

Final Report

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Acronyms

3A	awareness, appropriateness, audit
AIPES	Association of Imaging Producers & Equipment Suppliers
ALARA	As low as reasonably achievable
APAE	Applications of Particle Accelerators in Europe
BNCT	Boron Neutron Capture Therapy
CAGR	Compound Annual Growth Rate
CAPEX	Capital Expenditures
CCD	Charge-coupled device
CMOS	Complementary metal oxide semi-conductor
COCIR	European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry
CRT	Conformal Radiation Therapy
CT	Computed Tomography
DNA	Deoxyribosenucleic acid
DO	Dosimetrist
DRLs	Dose Reference Levels
EANM	European Association of Nuclear Medicine
EB	Electron beam
EBM	E-beam melting
EC	European Commission
ED-XRF	Energy dispersive X-ray fluorescence
EFSI	European Fund for Strategic Investments
EMA	European Medicines Agency
EO	Ethylene Oxide sterilization method
EOB	End of Bombardment
EOP	End of Processing
ESA	European Supply Agency
ESFRI	European Strategy Forum on Research Infrastructures
ESIF	European Structural and Investment Funds
ESR	European Society of Radiology
ESS	European Spallation Source
ESTRO	European Society for Radiotherapy and Oncology
FA	Fuel Assembly
FCR	Full Cost Recovery
GMP	Good Manufacturing Practices
GTRI	Global Threat Reduction Initiative
RERTR	Reduced Enrichment for Research and Test Reactors
HASS	High Activity Sealed Source
HDR	High Dose Rate Brachytherapy
HERCA	Heads of the European Radiological Protection Competent Authorities
HEU	Highly-Enriched Uranium
HLW	High Level Waste
IAEA	International Atomic Energy Agency
IBA	Ion Beam Implantation or Ion Beam Applications SA (Belgium)
IC	Integrated circuits
ICSD	Ionisation Chamber smoke detectors
IGRT	Image-Guided Radiation Therapy
ILW	Intermediate Level Waste
IMRT	Intensity Modulated Radiotherapy
IR	Ionizing Radiation
IT	Information Technology

IVD	In-Vitro Diagnostics
KET	Key Enabling Technology
LDR	Low Dose Rate Brachytherapy
LEU	Low Enriched Uranium
MEMS	Microelectromechanical systems
Mo-99	Molybdenum-99
MP	Medical Physicist
MRI	Magnetic Resonance Imaging
MS	Member State
NAA	Neutron Activation Analysis
NDE/NDT	Non-Destructive Examination/Testing
NM	Nuclear Medicine
NM/MI	Nuclear medicine/Molecular Imaging
NMR	Nuclear magnetic resonance
NP	Nanoparticle
NPP	Nuclear power plant
NTD	Neutron transmutation doping
OPEX	Operational Expenditures
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
PIXE	Particle Induced X-ray Emission
PM	Personalised Medicine
RBE	Radiobiological effectiveness
RCT	Randomized controlled trial
RF/RFQ	Radio Frequency Quadrupoles (cavities)
RI	Research Infrastructure
RN	Radiotherapy Nurses
RO	Radiation Oncologist
RP	Radiopharmaceuticals
RR	Research Reactor
RTT	Radiation Therapist
SAMIRA	Strategic Agenda for Medical, Industrial and Research Applications of nuclear and radiation technology
SBRT	Stereotactic body radiotherapy
SME	Small and medium-sized enterprises
SNMMI	Society for Nuclear Medicine and Molecular Imaging (USA)
SPECT	Single-photon emission computed tomography
SRS	Stereotactic radiosurgery
STEM	Science, Technology, Engineering and Mathematics
Tc-99m	Technetium-99m
US	Ultrasound
VHEE	Very High Energy Electrons
VLLW	Very Low-Level Waste
VMAT	Volumetric Arc Therapy
WHO	World Health Organization

Abstract

Since their discovery over a century ago, ionizing radiation (IR) technologies have become key tools to explore matter and biological building blocks. One of the most important discoveries of the 20th century — the structure of DNA — was the result of analysing its X-ray diffraction pattern. Over the years, health has become one of the most important non-energy applications to use IR, including imaging and therapy. IR is also used in many industrial domains, ranging from sterilization and disinfection to security-control systems, and from non-destructive testing to environmental applications. Nanotechnologies, nanoelectronics, photonics, advanced materials, biotechnologies and advanced manufacturing also use IR tools. Not only do these technologies generate high revenues by themselves, they also generate highly skilled innovation-oriented jobs, confer added value to products and services in which they are embedded and prompt other technological developments. Europe hosts a substantial infrastructure of facilities dedicated to fundamental or applied IR research, a broad network of advanced universities and research centres, as well as world-class industrial corporations and innovative SMEs competing at the global level. Such assets should be sustained and developed, alongside its most promising applications, while ensuring the highest level of safety and radiation protection. This report provides up-to-date information on the non-power applications of nuclear and radiation technology in the EU with the view of identifying their key societal benefits and development perspectives. The report proposes a series of actions in this area aimed at contributing to the European citizens' health and to the European economy, competitiveness, jobs and growth.

1. Executive Summary

Ionizing radiation (IR) technologies rely on charged particles beams (accelerators), X-Rays, α , β or γ -rays, and neutrons. Since their discovery more than a century ago, IR technologies have become key tools for exploring matter, improving health or supplying reliable and low-carbon energy. One of the most important discoveries of the 20th century — the structure of DNA — was the result of analysing its X-ray diffraction pattern. Over the years, Health has become the most important non-energy application area routinely using IR in imaging and therapeutic applications, complementing the two other imaging modalities, Magnetic Resonance and Ultrasound. Therapeutic applications using IR are developing and paving the way for personalised and targeted therapies. IR has also spread to many industrial domains, ranging from sterilization and disinfection to security-control systems, from non-destructive testing to environmental applications. Nanotechnologies, nanoelectronics, photonics, advanced materials, biotechnologies and advanced manufacturing use IR tools. Europe hosts a substantial infrastructure of facilities dedicated to fundamental or applied research, a broad network of advanced universities and research centres, as well as world-class industrial and innovative SMEs (Small and medium-sized enterprises), competing at the global level. This dynamic environment makes Europe a world leader in the development and use of IR technologies for the benefit of society. Such an asset should be fostered so as to continue to improve the quality of life for European citizens, while simultaneously generating employment and economic growth. To this end, much could be done to encourage technological development and to explore the benefits of IR technologies for purposes of providing many everyday applications, while ensuring the highest safety levels.

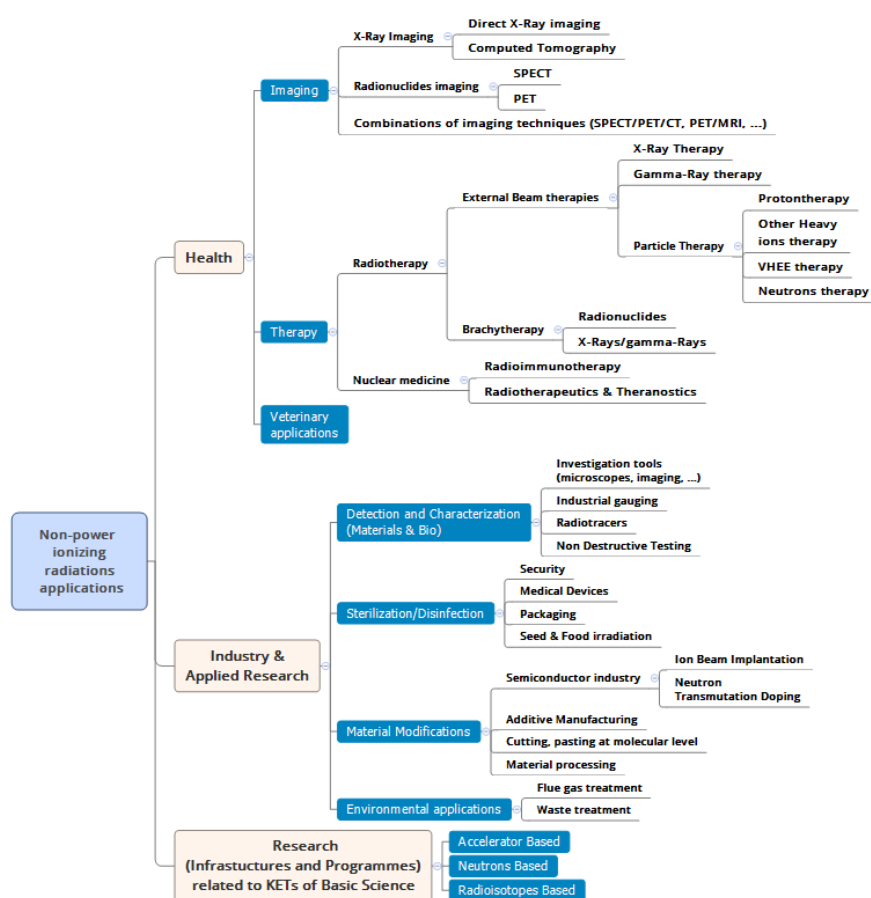


Figure 1: Global snapshot of non-energy applications of ionizing radiation

The economic impact of IR applications

IR-based tools are widely used in Health, Industry and Research. The “market” for these technologies extends from the IR tools and equipment themselves, to equipment servicing (maintenance, upgrades, training, etc.) and to health, industrial and research products and services in which they are embedded, and where their specific added value is most often difficult to isolate. This makes evaluating the market particularly challenging.

It has been estimated that the IR applications of accelerators alone underpin nearly half a trillion dollars’ worth of global commerce a year¹. The evaluation of the IR equipment market is somewhat easier. The world-market value of IR equipment can be evaluated at more than EUR 35 bn per year, with health applications being the most important non-energy sector. This global equipment market is attractive, with a high 3-6% annual growth rate and bright export prospects. The equipment market is also competitive, driven by constant innovation, which requires substantial investments.

IR applications create high added-value jobs in Health, Industry and Research fields for a highly-educated and well-trained work force. In EU-28 member states over 1,000,000 professionals are dose-monitored. The Health sector accounts for over 700,000 of such workers. The industrial sector (excluding nuclear energy), for 90,000 employees. In addition, the major European Health equipment companies employ over 60,000 individuals in Europe, a large number of whom work in the IR tools business, without accounting for the jobs induced along the supply chain. In addition, tens of thousands of jobs in smaller equipment-manufacturing companies, health institutions, laboratories, and industry & research centres depend indirectly upon these technologies.

Challenges in the Health domain

The three main medical specialties using IR-based tools are radiology, radiotherapy and nuclear (molecular) medicine. In these three domains, innovation is a constant driver that has two major focuses: reducing non-therapeutic individual radiation doses wherever possible and paving the way for developments in personalised medicine.

Radiology uses low energy external electron beams to produce X-Ray for imaging. Radiotherapy involves using higher energy external electron beams, γ -Rays or ion beams, or internal radioactive sources (“brachytherapy”) for treating tumours. Nuclear (molecular) medicine involves using radioisotopes injected into patients at low doses for functional imaging (SPECT/PET) to detect diseases and using other isotopes at high doses for the targeted therapy of tumours.

In the Health sector, imaging is of primary importance to enable making correct diagnoses and providing treatments. Medical imaging relies largely on IR, the use of which is constantly growing in Europe. Current numbers for the EU-28 are:

- 500 million radiographs per year (one per EU-28 citizen per year on average);
- 55 million² CT-scans (CT “Computed tomography”) procedures per year;
- About 10 million³ nuclear-medicine imaging procedures (SPECT “Single photon emission computed tomography” and PET “Positron Emission Tomography”) are performed per year.

¹ Robert W. Hamm (R&M Technical Enterprises, Inc.) and Dr. R. Kephart Director, Illinois Accelerator Research Center (IARC), Fermilab. Session TUIA2, IPAC17, Copenhagen Denmark

² Eurostat data.

IR is used therapeutically for various pathologies, e.g. for treating cancer, which is responsible for about 25% of the 5 million deaths per year in EU-28⁴ countries. It is estimated that about 50% of all cancer patients would benefit from radiotherapy during the course of their disease⁵.

All stakeholders (National Authorities, Scientific Societies, Equipment Manufacturers, Practitioners, etc.) recognise the issue of dose-exposure optimization for IR Imaging applications. Important advances were achieved over the two last decades, but efforts are ongoing to achieve further dose reduction.

Globally, about 20 per cent of the radiation doses received by the general public stem from “artificial”, “man-made” sources, of which almost all comes from health applications. In countries with high level of healthcare, health applications contribute close to 50 per cent of the population exposure to ionising radiation. Medical exposures have grown considerably in the past couple of decades, mostly due to the steep increase in the use of CT scanning and other advanced imaging⁶.

Echoing the WHO/IAEA 2012 Bonn Call for Action⁷, European medical professional organisations, equipment manufacturers and competent authorities have responded appropriately. Authorities have developed and implemented landmark regulations, namely the EC Basic Safety Standards⁸. CT equipment manufacturers, in collaboration with HERCA⁹, have developed and provided multiple dose-reduction features in CT systems for many years, and these developments continue today. Professional medical organizations are developing and harmonizing the “3A” (awareness, appropriateness, audit) approach, making extensive use of advanced IT and Big Data techniques¹⁰. These improvements also concern the radiotherapy sector, with equipment delivering X or γ -rays more accurately to tumours and combining imaging and therapy¹¹ techniques for personalised treatment planning.

These improvements raise also new challenges:

- The need to renew the ageing installed-equipment base. COCIR¹² stated that “a quarter of the European Computed Tomography (CT) installed base is unsuitable for the latest radiation dose-saving software upgrades, rendering around 3000 units obsolete and in need of replacement”¹³;

³ Approximate data because reliable statistics are not available.

⁴ http://gco.iarc.fr/today/online-analysis-pie?mode=cancer&mode_population=continents&population=990&sex=0&cancer=29&type=1&statistic=0&prevalence=0&color_palette=default

⁵ Radiotherapy equipment and departments in European countries: Final results from the ESTRO-HERO survey. Radiotherapy and Oncology 112 (2014)

⁶ The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008 Report to the general assembly, UNSCEAR, 2008

⁷ See proceedings of the 2012 Conference on “Radiation Protection in medicine: setting the scene for the next decade”. IAEA, 2015.

⁸ Directive 2013/59 Euratom.

⁹ Heads of the European Radiological Protection Competent Authorities. HERCA very recently issued (November 2017) a highly positive decisive paper about their collaboration with COCIR members. See CT Manufacturers Stakeholder Involvement (HERCA Report).

¹⁰ see the ESR’s EuroSafe Imaging action plan, for instance.

¹¹ Modern radiotherapy techniques, such as conformal radiotherapy, use imaging techniques to plan treatment closely using 3D so that x-rays are shaped to match the shape of the tumour.

¹² European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry.

¹³ Medical Imaging Equipment Age Profile & Density. COCIR, 2016. Page 5.

- An uneven distribution of equipment and the diversity of medical practices performed (e.g. dose reference levels, work organisation, etc.) among EU-28 Member States;
- The greater complexity of equipment and procedures raises questions about the adequacy of user education and training, and the organisation of work conducted inside medical departments¹⁴.

Professional bodies have taken initiatives to resolve these challenges^{15,16} such as the EuroSafe Imaging Action Plan:

EuroSafe Imaging Action Plan (2017)

1. Development of guidelines, implementation policies, and dissemination of a Clinical Decision Support system (ESR iGuide) in Europe;
2. Development of clinical diagnostic reference levels (DRLs) for adults and children;
3. Development of image-quality assessment based on clinical indications;
4. Promotion of dose-management systems to establish local DRLs;
5. Development of performance indicators for radiation-protection management;
6. Implementation of a clinical-audit tool for the use of imaging to improve the quality of patient care;
7. Radiation protection of children: development of guidance for an appropriate and safe use of imaging, and also of appropriate communication methods;
8. Dialogue with industry regarding improvement of radiological equipment, the use of up-to-date equipment (e.g. Dose Management Systems) and the harmonisation of safe exposure levels;
9. Strengthening the EuroSafe Imaging Stars network of imaging centres that embody best practice in radiation protection;
10. Organisation of radiation protection training courses and development of e-learning materials to promote a safety culture and raise awareness about radiation protection;
11. Facilitation of research into radiation-protection advanced topics (e.g. artificial intelligence), dissemination and translation into clinical practice;
12. Improvement of information for and communication with patients about radiological procedures, its related benefits and possible risks;
13. Engagement with stakeholders and collaboration with related initiatives and regulatory authorities in Europe and beyond to contribute to a global safety culture in medical imaging.

Such an action plan is typical of the initiatives taken by professional institutions concerned with IR applications across Europe (e.g. ESR, ESTRO, EANM, APAE, etc.). Nevertheless, the support of National Authorities remains necessary to ensure the corresponding required levels of investments are obtained. Such support may also take the form of transposing the recommendations of professional institutions into legal

¹⁴ See ESTRO/HERO Study.

¹⁵ e.g. ESR (European Society of Radiology) School and EuroSafe Imaging campaign, providing guidance and practical tools to help in compliance with the BSS Directive: ESR Clinical Audit Tool, ESR iGuide, Webinars, Educational material, Development of Diagnostic Reference Levels (DRLs).

¹⁶ e.g. ESTRO HERO initiative towards well-structured guidelines for capital and human resources. See also ESTRO School. See also note 5.

requirements over EU-28 nations, or incentives for implementing installation of improved equipment¹⁷.

IR tools are at the heart of major future innovations in Health Imaging and Therapy

Radiotherapy technologies are constantly improving¹⁸ and offer a wide spectrum of methods to treat many cancers. Besides photons (e.g. *X-Rays*, *γ-Rays*), protons¹⁹ and other ions (e.g. Particle Therapy) or neutrons can be more appropriate in some situations.

Particle therapy use is expanding worldwide. In the European Union, Proton therapy is already or will shortly be available in 13 member-states (Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Poland, the Slovak Republic, Spain, Sweden, and the United-Kingdom). At the moment, treatment using proton-beam therapy is more expensive than X-ray therapy and questions remain as to whether the additional patient benefit justifies the extra costs. EU Member States are conducting appropriate clinical studies to resolve this question. The EC could foster collaboration among Member States by establishing a common framework approach to clinical studies.

Another very promising area where IR tools may play a major role is “personalised medicine²⁰” (PM).

Personalised Medicine is a medical model using specialised tests, such as molecular imaging, to characterise each patient before tailoring the right therapeutic strategy for that person. The aim is to determine the patient’s predisposition to the disease, planned therapy and to deliver timely, appropriately targeted therapy. Personalized medicine could lead to better and more affordable medicine, avoiding ineffective treatments that can be detrimental to the patient and that waste valuable resources.

Radiology, radiotherapy and nuclear medicine are developing proactively in this direction, through equipment improvements and the initiatives outlined above, as well as thanks to encouragement via a coordination action plan funded by the EC (the “IC PerMed Secretariat”), which is aimed at establishing Europe as a global leader in personalised medicine research. Nuclear medicine offers considerable potential in this respect. The theranostics approach, where imaging and therapy are closely linked, in a customised manner, to increase the success rate of treatments and avoid unnecessary ones, may lead to cost savings for health systems²¹.

¹⁷ Such as in the USA, application of the National Electrical Manufacturers Association (NEMA) XR 29-13 “Standard Attributes on Computed Tomography (CT) Equipment Related to Dose Optimization and Management” is incentivized at reimbursement level.

¹⁸ e.g. ESTRO Vision. Radiotherapy and Oncology 103 (2012). Adaptive radiation therapy is an example of personalised medicine. In this treatment approach, frequent imaging is used to compensate for anatomical differences that occur over the course of treatment. Images are taken daily, or almost daily. When significant changes are observed, re-planning is considered.

¹⁹ More-focused energy delivery to the tumour, particularly useful when “organs at risk” are close to the tumour, or for children.

²⁰ Other terms that are used by the global community are “precision medicine,” “stratified medicine,” “individualized medicine,” “genomic medicine,” “pharmacogenomics,” and “P4 medicine” (for personalized, predictive, preventive, and participatory)

²¹ Nuclear medicine generally needs only few injections and can be administered in ambulatory care

In Nuclear Medicine, specific radioactive isotopes (the “payload”) are bound (“labelling”) to molecules (the targeting “vector”) which are designed to bind specifically with the targeted tumour cells. The payload may be an imaging radioisotope or a therapeutic one. “Theranostics” consists in using these compounds in combination. Injecting the imaging payload permits specifically screening each patient’s disease and assessing the likely efficacy of the treatment. Injecting the therapeutic compound next allows directly targeting and destroying characterised tumours. Finally, another imaging procedure enables checking the efficacy of the treatment.

The growth potential of theranostics is attested by the fact that, over the past few years, large pharmaceutical corporations^{22,23} have been investing heavily in this area or closely monitoring the work of smaller radiopharmaceutical-development companies²⁴, leading some market analysts to predict a sustained double-digit growth of this market over the 20 coming years.

Impediments to the development of nuclear medicine exist, however:

- while research and development (R&D) into therapeutic radiopharmaceuticals (RPs) is very active, R&D devoted to imaging RPs does not attract the same level of private investment: the return on investment is deemed insufficient due to historically-low reimbursement levels for imaging RPs. Yet, the development of new imaging compounds is key to extending the potential of nuclear medicine into new clinical indications. Incentivising “in-house” development and labelling may circumvent the lack of development of new imaging vectors. Indeed, Authorities could allow public institutions like hospitals, medical schools and laboratories to develop “in-house” labelled imaging compounds, using more “liberal” rules than in the conventional process of therapeutic-drug development. This could encompass Phase I development trials, in particular, until commercial companies can take over Phase II-III clinical trials. This would reduce the costs of the research phase while stimulating clinical research²⁵. Such a more “liberal” process would not preclude the need for “GMP²⁶-like” processes.
- nuclear medicine can develop only if the sustainability of the radioisotopes supply chain is ensured. This supply chain must remain versatile (able to mass-produce all necessary radioisotopes), of high quality (manufactured under GMP or “Good Manufacturing Practices”), reliable, affordable and available worldwide. Research reactors²⁷ currently produce the majority of both diagnostic and therapeutic radioisotopes, including the most used imaging radioisotope Mo-99/Tc-99m. This study allowed to confirm the conclusions of the market analysts, AIPES and OECD/NEA: demand for Mo-99/Tc-99m should remain stable in Europe until 2030. This means that European research reactors, among them HFR (The Netherlands), BR2 (Belgium), Maria (Poland) and LVR-15 (Czech Republic), will remain important Mo-99 producers, delivering more than about 60% of the global

²² For instance, 4 years after receiving European and US market approvals (2013), the Bayer Xofigo® drug revenues are already over 400 M€

²³ For instance, Novartis acquired AAA in 2017, a French radiopharmaceutical development company, which just got the market approval for EU and USA for a Lutetium 177 compound (Luthatera®)

²⁴ For instance, Johnson & Johnson Innovation supports the development of a radiopharmaceutical based on Actinium-225

²⁵ Present and future of PET-radiopharmaceuticals, Philip H. Elsinga, Nuclear Medicine Review 2012, 15, Suppl. C: C13–C16.

²⁶ GMP : “good manufacturing practices”.

²⁷ Medical isotopes. Global importance and opportunities for the Netherlands in a European context. Nucleair Netherlands, 2017, page 21.

demand. However, all these reactors face technical issues related to ageing, require regular updates, refurbishment or replacement and their lifetime cannot be indefinitely extended. OECD/NEA and the European Observatory on the Supply of Medical Radioisotopes have been warning decision-makers for several years about the potential risks of a global shortage of medical radioisotopes. The analysis and scenarios developed in this study (see A.13) suggest that only a dedicated (European) multi-radioisotope-production reactor will support a cost-efficient, reliable, versatile, GMP (good manufacturing practice) and mass-production supply chain. Because of the potential importance of radioisotopes for the health of EU citizens, for cost savings to health systems, for EU economic growth and for high technology jobs, EU Authorities should support investment in this area.

Beyond these imaging-compound development and supply chain actions, other initiatives to be taken are

- In the regulatory domain: increasing the development, production and dissemination of clinical guidance documents, including appropriate usage criteria; improving knowledge and understanding among those developing new radiotracers and radiotherapeutics about the type of evidence EMA and national Market Authorities require to approve them as safe, effective, reasonable and necessary; communicate with these bodies for regulatory approval of emerging agents that are safe and effective; and continually promoting the work that is being done in the field to foster greater understanding and support of Nuclear Medicine/Molecular Imaging (NM/MI) in legislative and regulatory venues.
- Ensuring adequate and appropriate reimbursement for NM/MI procedures by the Health-care reimbursement systems; working with all stakeholders (including insurance firms) to optimize reimbursement of current and future agents.
- In the educational field: increasing the supply of qualified personnel (practitioners, medical physicists, technologists, radiopharmacists, biologists in the Health sector, but also design and manufacturing engineers, etc.); increasing awareness of NM/MI as an appealing and rewarding field for students interested in STEM careers.
- For the public: promoting greater understanding of radiation benefits and levels among the general public and in the medical field.

Such initiatives are first and foremost the professional bodies' responsibility (EANM, National NM societies...), but public support may be particularly useful, in the form of organization of events gathering all involved stakeholders, or communication actions, for instance.

Even if research reactors, including BR2 in Belgium, FRM-II in Germany or HFR in the Netherlands, are forging links with medicine, pharmacy and equipment researchers and developers, it seems that these initiatives are not commensurate with the large existing European campuses devoted to sciences and technologies using accelerators and neutrons sources. Considering what is at stake here, both in terms of public health and Healthcare systems, Authorities should consider the opportunity of funding such European Centre(s) of Excellence for Nuclear Medicine. To move in this direction, a Health Technology Assessment of emerging Nuclear-Medicine applications seems opportune. It is recommended that such an HTA be rapidly conducted with EC support.

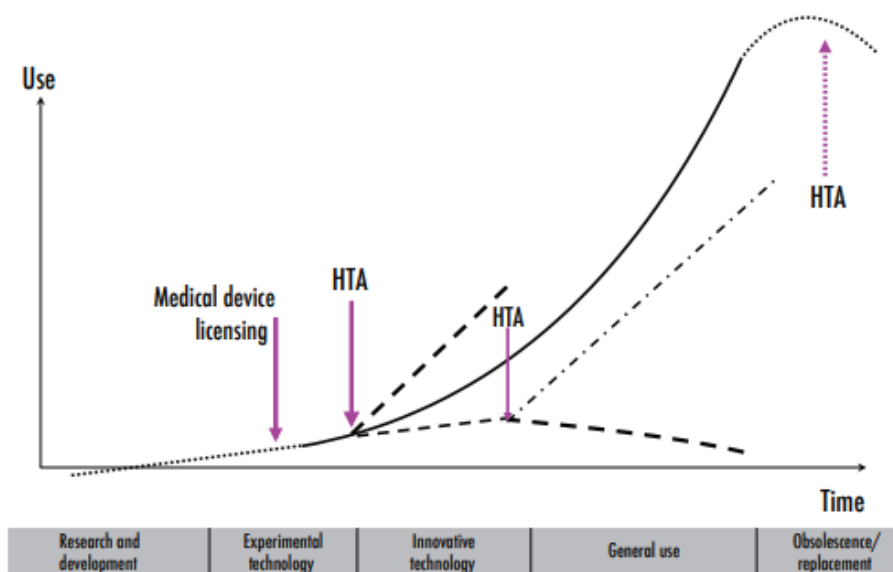


Figure 2: Health technology assessment and diffusion of Health technologies²⁸

Beyond their extensive use in medicine, IR-based tools are present in a wide variety of applications in Industry, Applied Research, Agriculture, Environment or in Security

Detection and Characterization applications

...in the Industry and applied sciences	Non-destructive testing, Process instrumentation & gauges (thickness, level, density, moisture), Spectrometers, chromatographs, gas or explosives detectors, and a large variety of microscopes, but also neutron radiography and activation analysis, carbon dating, etc.
... in the Environment	Environmental tracers, Water resource management, etc.
... in security	X-Rays, γ-Rays or fast neutron scanning devices used in public locations

Sterilisation and Disinfection applications

...in the Healthcare field	Syringes, surgical gloves, gowns, masks, plasters, dressings, bottle teats for premature babies, artificial joints, and raw materials for pharmaceuticals and cosmetics are sterilised with ionizing-radiation devices; 50% of single-use medical devices (such as syringes and scalpels) in the UK, and 40 to 50% of all disposable medical products manufactured in North America are sterilised using ionising-radiation devices; Smart packaging is increasingly sterilised in this way; The encapsulation of electronics into packaging or medical material increases the demand for safe and reliable sterilisation technologies that guarantee the required reduction in bio-burden pathogens. Only very low-energy electrons with a precisely-adjusted penetration depth can be used for sterilising products without destroying any sensitive electronics inside or degrading basic layers of the composite materials.
...in Industry	Insect control, food irradiation, seed treatment, disinfection of grains, nuts and spices.
...in Agriculture	For the conservation of books, archives and artefacts
...in Heritage preservation	

²⁸ Health technology assessment of medical devices. WHO 2011

Material processing and modifications applications

	For semiconductor material modification (ion-beam implantation or, less commonly, neutron-transmutation doping);
	for advanced manufacturing processes (welding, additive manufacturing, structured sintering, e-beam melting, etc.);
...in industry	for cutting, linking and pasting at the molecular level, 2D printing (food packaging), 3D printing, lacquering and coating, and grafting;
	for polymer modifications, such as cross-linking polymers for wires and cable insulation, for heat and abrasion resistance, for pre-vulcanization: 92% of all tyres in the world are treated in this way.
... and environmental applications	waste treatment, flue-gas treatment...

Table 1: Applications using Ionizing radiations in Industry, Applied Science, Agriculture, Environment and Security

The growth potential for novel industrial applications based on IR tools is attested by the number of ongoing research actions^{29,30,31,32,33}. Nanoparticles (NPs) and nanostructures manufactured with IR tools may, for instance, be used in a number of areas. Additive manufacturing, where complex structures are built by adding successive melted layers, is a reality. Recent advances in particle-accelerator technology could be beneficial for many energy and environmental applications, such as treating drinking water, waste water and sludge, removing pollutants from stack gases, treating medical waste, conducting environmental remediation of hydrocarbon- contaminated soil and fossil-fuel conversion. They may also have synergetic effects in other strategic domains (magnetic separation and superconducting technologies), i.e. increasing the capacity of wind generators, enhancing the magnetic separation of material streams, and increasing the efficiency of electrical-power transmission.

IR technologies operate in a complex environment with national regulations and industrial constraints. Both the technical performance and economic competitiveness of these technologies are critical for their successful adoption. In addition to these factors, other forces are at play, including the regulatory landscape, public perception of new technologies and market incumbency of existing technologies. In the case of seed and food irradiation, for instance, e-beam treatment is superior to other microbial-inactivation technologies because there is no change in taste (steaming and chemical treatment change the taste), texture (steam changes the texture, usually making the product unusable) and colour, and leaves no toxic residue. In addition, the treatment can be designed as an in-line process, scalable to low-volume producers as well as for mass-production, while the technology uses only one-tenth of the energy consumed by steaming. However, the main limitation for food sterilisation is regulatory, and European laws and regulations governing ionising radiation of food depend on Member States and may appear obsolete as compared to applicable regulations in other countries. It is recommended that the European policy on this subject be revisited and harmonized³⁴.

Beyond immediate industrial applications, large Research Infrastructure (RI) and Research programmes are key for maintaining the EU's competitive world position and for attracting and developing skills.

²⁹ See Nanoscale Radiation Engineering of Advanced Materials for Potential Biomedical Applications. IAEA Radiation Technology Report N°5 and many other IAEA technical reports.

³⁰ See IAEA's International Conference on Applications of Radiation Science and Technology (ICARST 2017) proceedings.

³¹ See 8th International Particle Accelerator Conference (IPAC 2017) proceedings.

³² See APAC/EUCARD2 Final report, 2017.

³³ See US DOE Workshop on Energy and Environmental Applications of Accelerators, 2015.

³⁴ Regulations applicable in Europe are Directives 1999/2 & 3/EC and applicable national laws

IR Research uses accelerators, neutrons beams and radioisotopes. Major analytical facilities exist in Europe for accelerator-based and neutron-based research, in Harwell (UK)³⁵, Saclay³⁶ and Grenoble³⁷ (France), Hamburg (Germany)³⁸, Trieste (Italy)³⁹, Lund (Sweden)⁴⁰, the PSI at Villigen⁴¹ and CERN in Switzerland, among many others, and tomorrow ITER. These campuses represent key hubs for various research activities and open innovation hubs for developing services and industrial products.

With EC support, ESFRI (European Strategy Forum on Research Infrastructure) is a key tool for policy-making on Research Infrastructure in Europe. ESFRI enables strengthening the European Research Area (ERA) and it regularly updates its roadmap. ESFRI Projects and ESFRI Landmarks may have access to financing from the EU (e.g. Horizon 2020, ESIF, EFSI, etc.). A series of projects concerning IR applications are included in the ESFRI 2016 Roadmap. ESFRI is currently preparing its 2018 Roadmap and additional actions may be required in the IR field.

Accelerator-based research

In the accelerators field, the final report from the APAE/EUCARD2 details the actions to be taken at European level by all stakeholders (National/Public Authorities, scientific societies, industrial players, accelerators users, etc.) to develop accelerator-based applications for the greater benefit of the European community. These actions are summarized below:

APAE/EUCARD2 Recommendations

Developing Compact accelerators: More compact accelerator technology is a key factor in all applications. In this sense, the medium-term development of superconducting components is crucial. In the longer term, laser and terahertz acceleration techniques could potentially offer a dramatic reduction in size, although significant development is still needed to establish if this reduction can be achieved in a suitable environment.

Improving designs and cost-effectiveness: Many accelerator applications require simpler and lower-cost designs and concepts, with higher efficiency, reliability, robustness, and reduced costs of operation, more specifically in healthcare, industry and security; in fact, the “ready-mobility” of accelerator equipment is a growing need for some applications.

Improving academia-industry interaction: The development of accelerators for “big science”⁴² drives the majority of advances in accelerator R&D worldwide. Manufacturers of accelerators for industrial and other uses are often not well connected to these efforts. Programmes are required to better connect commercial accelerator groups, research facilities, universities and health centres.

Improving student training and knowledge-transfer: Basic education and training of students in relevant fields are essential to increase the flow of a suitably trained workforce into manufacturing industries and accelerator- technology applications;

³⁵ ISIS Neutron and Muon source, DIAMOND synchrotron light source and the Central Laser Facility CLF.

³⁶ Laboratoire Leon Brillouin and SOLEIL synchrotron.

³⁷ European Synchrotron Facility, Institut Laue-Langevin and EMBL, European Molecular Biology Laboratory.

³⁸ EUXFEL, PETRA III and free electron laser FLASH.

³⁹ Elettra synchrotron, FERMI@Elettra and ICTP, International Centre for Theoretical Physics.

⁴⁰ ESS European Spallation Source and MAX-IV.

⁴¹ SINQ, SLS and SwissFEL.

⁴² Large-scale projects usually funded by national governments or groups of governments.

appropriate knowledge-transfer into industry is also essential.

Improving public understanding of accelerators and their underlying science: Investing in improving public understanding of accelerator science and applications is needed, as along with a better-informed perception of any risks.

Improved R&D collaboration within the EU: A stronger coordination of R&D efforts and collaborations at EU level would be highly beneficial.

Neutrons-based research

As a complement to accelerator-based research, neutron scattering covers an extremely wide range of disciplines: from fundamental physics, through chemistry, materials, and biology, right through to interdisciplinary areas such as engineering and archaeology. Neutron beams are versatile and irreplaceable tools and have a strong record of being used both to make scientific discoveries and to develop technology in a number of domains. Neutrons beams are produced in research reactors or spallation sources. The USA, Japan, Korea, Australia and China rely upon powerful neutron sources. Stressing the importance of neutron sources in a number of essential research domains and stating that the “instrument-days” potential, which quantifies the “productivity” of installations, will be dramatically reduced in the future, the Neutron Landscape Working Group of ESFRI⁴³ has identified a series of challenges, which a collective European strategy should address.

Challenges identified by ESFRI Neutron Landscape Group

1. Developing, without delay, a growth plan for the European Spallation Source (ESS) that provides for more than the 22 planned instruments and committing secure funding in order to achieve this goal.
2. Examining the opportunities available to invest in the broad neutron pool in Europe: implementation of an upgrade programme for the 4-to-5 newest current sources, ESS (Sweden), ILL(France), ISIS (UK), MLZ (Germany) and PSI (Switzerland), that can be operated beyond 2030.
3. Maintaining the ILL’s world-leading scientific output over an extended period working together with the ESS by providing political and financial support.
4. Establishing courses for the development of new, medium power high-brilliance neutron facilities.
5. Mobilising the European neutron-user community so that, in partnership with the sources, they act concertedly to secure the future health of the discipline.
6. Exploring the feasibility of setting up a more coherent and coordinated ad-hoc strategy group at pan-European level to develop a collective perspective and oversee the long-term sustainability of Europe’s neutron sources.
7. Current source facilities are urged to examine their operating regimen and reinvent themselves by implementing best practices from other disciplines.
8. Developing an Open Access to Data policy and identifying neutron-scattering mechanisms as part of a broader initiative to elaborate investigative analytical methods as applied to the materials sciences.
9. Launching a study about a “next generation” world-leading European neutron source that would be commissioned in the second half of the century; exploring possible global partnerships.

⁴³ Neutron scattering facilities in Europe. Present status and future perspectives. ESFRI Physical Sciences and Engineering Strategy Working Group. Neutron Landscape Group. June 2016

The availability of skilled personnel is a cross-disciplinary concern, in Health, Industry and Research using IR tools

A wide range of skilled personnel (*researchers, engineers and technicians, technologists, radiologists, medical physicists, dosimetry specialists, nurses, etc.*) are needed to implement non-energy ionizing radiation applications. The medium-term threat of a skilled-personnel shortage is shared by European Institutions⁴⁴, as well as by Health, Industry and Research stakeholders, all echoing the same finding in the nuclear-energy field (EC/JRC⁴⁵). This potential cross-disciplinary shortage of skills jeopardizes the sustainability and safe development of such applications.

Large Research Infrastructure and programmes provide an internationally competitive environment. Combined with the regular turnover of visiting researchers and facility users in this infrastructure, they offer unique training potential for young researchers, technicians, managers and advanced technology developers. Simultaneously, the disaffection of European students for STEM (Science, Technology, Engineering and Mathematics), and even more so for IR science and technologies, must be overcome in order to attract the necessary talents. Professional societies, research institutions and manufacturers have developed their own initiatives⁴⁶. It is recommended that the EC/JRC study on availability of skilled personnel in the nuclear industry be repeated in the non-energy IR domain, to assess whether EU actions in this area such as the European Credit System for Vocational Education and Training (ECVET), ERC, MSCA or ERASMUS+ grants and projects are sufficient.

IR technologies contribute to the development of the five “KETs” in Europe

In his political-guideline document for the new European Commission, President Juncker said “[...] we need to maintain a strong and high performing industrial base [...]. To achieve this, we need to stimulate investment in new technologies [...]”. Commissioner Bieńkowska, in charge of the Internal Market, Industry, Entrepreneurship and SMEs, stated, “Together with the Commissioner for Research, Science and Innovation, I want to use the Horizon 2020 Programme and other EU policy instruments in order to support close to market industrial innovation and key enabling technologies”. Commissioner Moedas, in charge of Research, Science and Innovation, stated, “We must prioritise commercialisation. Turning science into technology. Bringing technology to market”⁴⁷.

In 2015, the High-Level Group on Key Enabling Technologies (KETs) identified five KETs, which were considered as strategically most relevant with regard to the general objective of European reindustrialization:

- NT (nanotechnology);
- MNE (micro- and Nano electronics, including semiconductors);
- PHOT (photonics);
- AM (advanced materials);
- IB (biotechnology).

⁴⁴ Cedefop (European Centre for the Development of Vocational Training/ DG Employment, Social Affairs & Inclusion) studies, or the periodic European Vacancy and Recruitment Reports (same DG), or Labour Market Shortage in the EU (DG for internal policies), or professional bodies studies like the ESTRO/HERO study, etc.

⁴⁵ Putting the supply and demand for nuclear experts by 2020 within the EU nuclear energy sector into perspective. JRC Scientific and Policy Report, 2012.

⁴⁶ e.g. European School of Radiology, European School of Multimodality Imaging & Therapy, ESTRO School, CERN Accelerator School, Siemens Healthineers Academy, etc..

⁴⁷ HLG on Key Enabling Technologies. KETs: Time to act. Final Report. June 2015.

A sixth, and more overarching KET was added to include the manufacturing side of the industry: AMT (advanced manufacturing technologies)⁴⁸.

Radiation-based technologies have not been retained among the “key enabling technologies” by themselves, despite the fact that, in complement to their own achievements, they provide powerful tools underpinning the development of all six KETs: nanotechnology, nanoelectronics, photonics, advanced material characterization, treatment or manufacturing and obviously biotechnologies.

	Charged-particle beams (accelerators)	X-Rays	Radioisotopes (α , β , γ emitters)	Neutrons
All KETs	all radiation modalities used for material/biological properties investigations for all KETs			
IB (biotechnology).	Nuclear medicine, advanced imaging and therapy			
AM (advanced materials);	Material processing			
AMT (advanced manufacturing technologies)	Additive manufacturing	Quality control	Industrial gauging Quality control	Quality control
NT (nanotechnology);	Polymers cross-linking			
MNE (micro- and nanoelectronics)	Ion implantation EUV, VUV lithography	Metrology & Quality control		
PHOT (photonics);	Synchrotron, free electron lasers (FEL)			

Table 2: Relation between KETs and radiation technologies

So that policy-makers can readily appreciate the broader picture with respect to the huge benefits of IR technologies for EU-28 health and wealth, and the potential encouraged by supporting research, development and the use of these technologies, it is recommended that a further study be conducted to assess and quantify to what extent IR technologies underpin KETs development.

Statistics collected on the use of IR technologies in EU-28 Member States vary widely from one country to another. It is recommended that the Member States should back the development of reliable standardized databases across the EU-28 for all applications using IR.

The data-mining portion of this study has shown the difficulty in retrieving precise, homogeneous, standardised and complete quantitative data for the EU-28 in almost all the areas of interest. Even when incomplete data exist, attempts at contrasting MS-specific situations have shown that making any statistical assessments is problematic. As a consequence, much of the data presented in this report is fragmentary, concerning only a part of EU-28 Member States, or presenting inconsistencies between the different databases used. For each set of data, the coverage is indicated, as are inconsistencies, when appropriate.

However, as solid quantitative information is a prerequisite for developing a consensus on strategic issues and decisions, a general recommendation is that the Member States should pursue the task of developing reliable, homogeneous, standardised and specific EU-28 databases in the key areas addressed in this study, namely in the Healthcare field.

⁴⁸ Horizon 2020: Key Enabling Technologies (KETs), Booster for European Leadership in the manufacturing sector. EC/DG for Internal Policies. 2014.

2. Foreword

2.1. Acknowledgments

This report has been prepared by NucAdvisor and Technopolis Group through the support of many Scientific Societies across EU-28 and Experts on the different topics covered by the study.

Authors would gratefully like to acknowledge all the participants that contributed to collecting information about EU-28 perspectives regarding the use of non-power IR applications, with special thanks to the SAMIRA Advisory Panel.

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2.2. Validation Process / Advisory Panel

2.2.1. Quantitative data validation

In order to validate the quantitative data reported in this study, a careful and independent check of all figures has been conducted. A NucAdvisor engineer, who was not mobilized by the SAMIRA works, checked for consistency between the data given in the report and the data sources themselves.

Solid quantitative information is key to reaching consensus about strategic issues and decisions. The data-mining portion of this study has shown the difficulty of finding precise, homogeneous, standardized and complete quantitative data for the EU-28 in almost all the areas of interest concerning ionizing- radiation applications. Even when incomplete data exist, contrasting MS-specific situations —when they are not intra-MS specific — make any statistical treatment hazardous. Hence, a general recommendation is that the Eurostat should pursue the task of constituting reliable, homogeneous and standardized EU-28 databases in the areas addressed in this study, particularly in the Healthcare field.

2.2.2. Outcomes validation

In order to validate the general outlines and all the views relative to the specific areas addressed in this report, a high-level validation process by an Advisory Panel has been adopted. Individuals appointed by the solicited body were interviewed about specific points and they reviewed the relevant parts of this report.

The Advisory Panel was composed of:

- Mr. Charlton Kevin – OECD Nuclear Energy Agency (OECD NEA)
- Mr. Corridori Riccardo - COCIR
- Prof. Deconinck Frank - European Nuclear Society (ENS)
- Mr. De Haas Geert - European Nuclear Society (ENS)
- Dr. Faus-Golfe Angeles –APAE (Applications of Particle Accelerators in Europe)
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- Mr. Solente Nicolas - Club of Agencies
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Some institutions have submitted written comments (see appendix 24).

2.3. Structure of this report

This report provides a detailed landscape of the different IR applications in the Health, Industry and Research fields.

A global snapshot of ionizing radiation-based applications is provided in Chapter 4. Chapter 5 is devoted to the economic impact of IR-based applications at global and European level, for Health, Industrial and Research applications.

In chapters 6 to 9, the challenges, gaps, and the measures for addressing these challenges and gaps are identified for each key-application: in Health (Chapter 6), Industry and Research (Chapter 7), Spent Fuel and Radioactive Waste Management (Chapter 8) and Safety (Chapter 9).

Chapter 10 summarizes the recommendations which can be drawn from this study.

For the convenience of the reader, technical details and specific points are addressed in the appendixes.

2.4. General considerations for readers

As concerns radioactive wastes, when quotations are provided in the report (volumes and activities), if no information is provided on the radionuclide(s) concerned then the waste categorization used (e.g. High-Level Waste, Intermediate Long-lived Waste...) is the one of the country concerned by the radioactive wastes. Each Member State having its own Radioactive Waste categorization, it is necessary to refer to the national definition of each category.

3. Introduction

Since their discovery more than a century ago, ionizing-radiation technologies have become invaluable and irreplaceable tools for exploring matter, supplying low carbon energy or improving Health. One of the most important discoveries of the 20th century — the structure of DNA — resulted from analysing its X-ray diffraction pattern. Over the years, Health has become the most important non-energy fields to routinely use ionizing-radiations technologies for the benefit of mankind. X-Ray imaging is an ideal complement to Magnetic Resonance and Ultrasound in diagnostics. Therapeutic applications of ionizing radiation are constantly increasing, becoming more focused, more precise and efficient. The number of medical radiological procedures in Europe runs into hundreds of millions per year (~400-500 million per year), and the healthcare sector employs more than two-thirds of the one million European radiation workers. Several well-known European companies and many small and medium-size European enterprises operate in the European medical radiological equipment market. New progresses in nuclear medicine, combining imaging and therapy, are paving the way for promising targeted cancer treatments.

The medical sector is responsible for an overwhelming majority of the exposure European citizens have to man-made radiation. Population radiation-exposure levels from medical applications have grown considerably over the past couple of decades, mainly due to the increasing use of computed tomography (CT). Means to lower the level of radiation exposure of both the public and medical-staff members exist, like improved equipment, or avoid unnecessary exams, but awareness attitudes remain to be developed and investment gaps remain to be filled.

About forty research reactors are in operation in the European Union (EU) and some important investments in new capacity are planned or underway. Research reactors play an essential role in the supply of radioisotopes for medicine, in advanced-materials testing and other non-power areas. The European research-reactor inventory is, on average, over forty years old and prone to unplanned outages. The situation is especially worrisome in relation to the production of the most widely used medical radioisotope, Molybdenum-99 / Technetium-99m (Mo-99 / Tc-99m), which relies on a small number of reactors and a generally-fragile production infrastructure. The supply of Mo-99 / Tc-99m was repeatedly disrupted between 2008 and 2010. Even if initiatives to coordinate reactor outages and bring some additional irradiation capacity have managed to avoid severe disruptions in recent years, there is a need for investment in further production capacity in order to avoid Mo-99 / Tc-99m shortages from 2025-2030, and to meet the future demand for promising therapeutic radioisotopes like Lutetium-177 (Lu-177).

Europe hosts a substantial infrastructure of laboratories dedicated to fundamental or applied research, a broad network of advanced universities and research centres, as well as world-class industrial SMEs. This dynamic environment makes Europe a world-leader in developing and utilising ionizing-radiation technologies for the benefit of society. Such an asset should be developed for purposes of improving the quality of life of European citizens, while generating employment and economic growth.

However, the disaffection for nuclear matters in Europe is a real threat. Scientific careers and notably in the ionizing-radiation field are attracting fewer students. From the societal standpoint, it is necessary to raise awareness about the potential of ionizing-radiation technologies in terms of health and economic growth amongst decision-makers and the general public. Increasing public acceptance of these key technologies and showing the public that their associated risks are correctly assessed and under control in modern applications is key.

Much remains to be done to achieve such results, both in terms of technological development as well as by exploring the benefits of ionizing-radiation technologies in many everyday applications.

Many European policies and initiatives have an influence on the various applications of nuclear and radiation technology in medicine, industry and research. The DG ENER is in charge of the European nuclear-energy policy, including radiation protection, nuclear safety and safeguards, management of radioactive waste and spent fuel, as well as the decommissioning of nuclear facilities. The most recent developments in the European nuclear-energy policy area of relevance to the medical, industrial and research applications of nuclear and radiation technology include major landmark EU legislation. This encompasses Nuclear Safety (Council Directive 2014/87/Euratom), radioactive waste and spent-fuel management (Council Directive 2011/70/Euratom) and radiation protection (Council Directive 2013/59/Euratom) to which should be added the April 2014 Communication on a Nuclear Illustrative Programme (PINC), which also includes research reactors.

The Euratom Supply Agency (ESA) is assigned the task of ensuring a regular and equitable supply of nuclear fuels to EU users. ESA also manages the European Observatory on the security of the supply of medical radioisotopes. Other relevant European policy areas include research and innovation, health and the internal market.

Notwithstanding the general understanding of the importance of nuclear and radiation technology in the medical, industrial and research fields, and the related existing European initiatives and policies in this respect, the non-power applications have as yet not been subject to any systematic and coordinated evaluation by the Commission agencies. There is, in particular, a need to address the issues relating to the security of the supply of Molybdenum-99 and other radioisotopes for medical use in the post-2025 period.

In order to fill these gaps, the DG ENER has decided to embark on developing a Strategic Agenda for Medical, Industrial and Research Applications of Nuclear and Radiation Technology (SAMIRA), which should be supplied in 2018. The SAMIRA proposal should serve to define the Commission's views on the major issues relating to the use of nuclear and radiation technology outside the nuclear-energy sector. This study is part of the preparatory work for developing SAMIRA.

The objective of the present study is to provide the Commission with up-to-date information on non-power uses of nuclear and radiation technology in the EU. The study analyses both the current state of play in this area and the development perspectives of the market for nuclear non-power goods and services, with a particular focus on the supply of radioisotopes for medical uses.

In this report, the major ionizing-radiation technologies are described, along with their potential in the medical, industrial and research sectors. A series of actions is proposed, which could help to develop important assets for the greater benefit of European citizens' health and for the European economy, competitiveness, jobs and growth.

4. Global snapshot of non-energy ionizing radiation applications

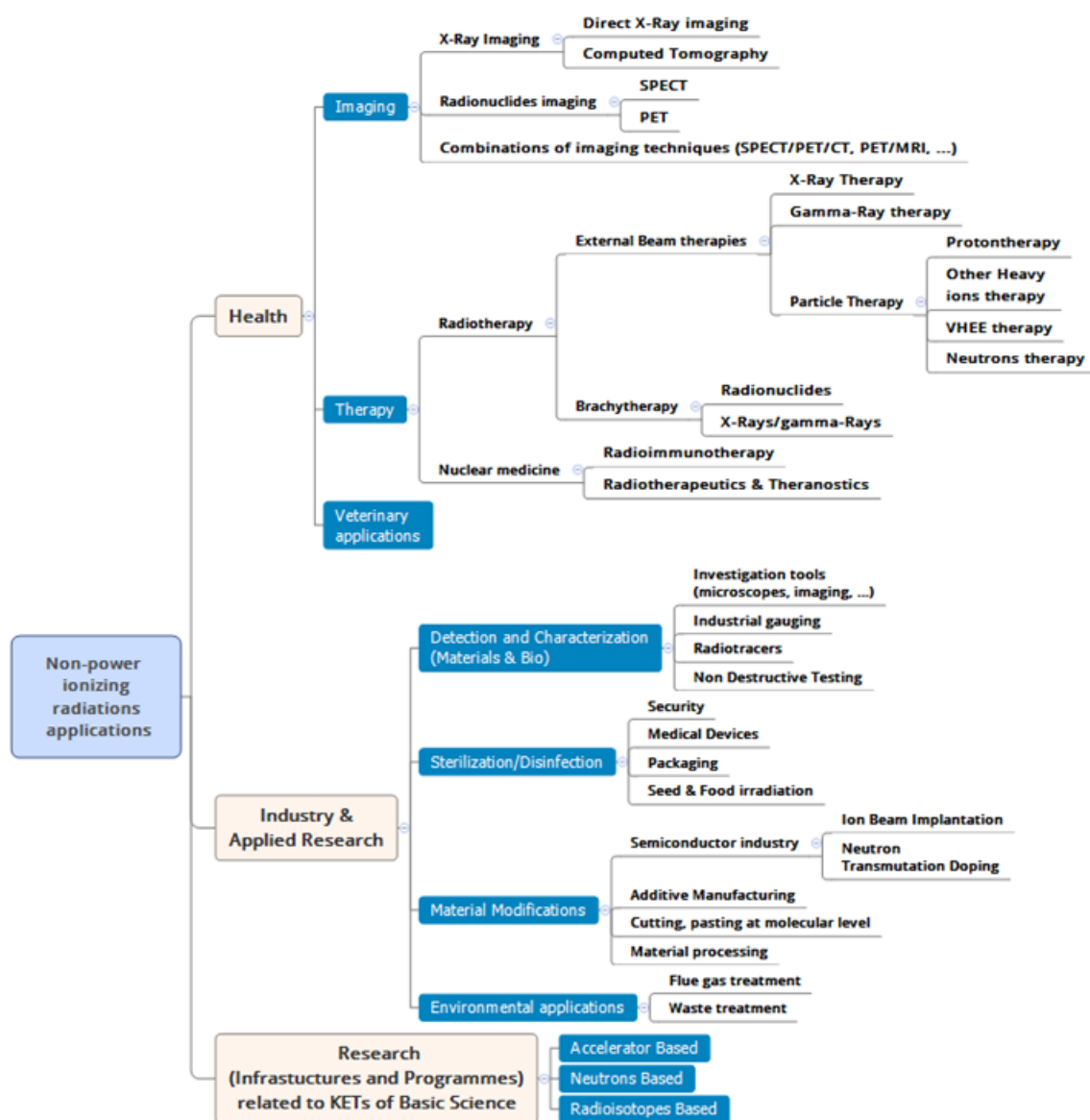


Figure 3: Global snapshot of non-energy applications of ionizing radiation

Ionizing radiation technologies are used daily in Europe in a number of fields: Health, Industry and Research, with high impact on the health of European citizens, European economy and international influence. For instance,

In medicine...

After the discoveries of non-energy radiation use in medicine at the end of the 19th century⁴⁹, these technologies quickly became widely used in Health Imaging and Therapy. Each of the 500 million EU-28 citizens benefit on average from more than one radiography procedure each year, whether at the dentist's, for chest/thorax imaging, for breast-cancer screening programmes or through computed tomography (CT).

⁴⁹ X-Ray application discovered by Röntgen 1895

Every year, more than 55 million CT procedures are performed in the EU-28. About 10 million nuclear medicine imaging procedures (*SPECT - Single photon emission computed tomography and PET - Positron Emission Tomography*) are performed every year, sometimes combined with CT or Magnetic Resonance Imaging (MRI).

Ionizing-radiation technologies are widely used for cancer therapy. Cancer is responsible for about 25% of the 5 million deaths per year in EU-28⁵⁰. Experts estimate that about 50% of all cancer patients would benefit from radiotherapy during the course of their disease⁵¹. Nuclear medicine promises advanced cancer treatments, paving the way for a real “personalised medicine”. Such personalized cancer treatments could increase therapy success rates, avoid useless treatment trials and lead to potential savings for health systems.

In all Healthcare areas, constant progress is being made for the greater benefit of the health of European citizens. Innovation is key and is the maxim of European researchers, laboratories, and industrial champions, whether world-class players or SMEs.

In Security...

For purposes of ensuring security, ionizing radiation devices are used daily in public locations (airports, harbours, public buildings, etc.) and are constantly evolving towards improved precision. For instance, over two billion tons of cargo pass through ports and waterways annually in the United States. Many ports rely on gamma-ray scanners, based on radioactive isotopes such as cobalt-60, to screen cargo for nuclear materials or weapons. An increasing number are turning to high-energy X-rays generated by particle accelerators to keep ports safe and to prevent contraband from entering the country. Other methods for scanning cargo are being developed, such as “neutron interrogation”. Neutron-investigated matter responds by giving off gamma rays, which are characteristic of the material, thereby allowing for better definition of the composition of the cargo.

For material processing...

A number of industrial applications use ionizing radiation. The semiconductor industry, for instance, makes extensive use of ion implantation. Power electronics uses neutron transmutation doped (NTD) silicon. The Radial-tyre manufacturing process relies largely on electron beams to prevent material-thickness reduction or displacement. With its unique advantages, electron-beam welding is used for automobile, aerospace, medical and other industrial parts. E-beams also allow for advanced manufacturing processes like “e-beam melting”⁵² among many other applications.

For sterilization and disinfection...

The sterilisation of expensive and sensitive pharmaceuticals and smart packaging is of growing importance. Syringes, surgical gloves, gowns, masks, plasters, dressings, bottle teats for premature babies, artificial joints, food packaging, raw materials for pharmaceuticals and cosmetics, and even wine corks are sterilised in this way. About 40 to 50% of single-use medical devices (such as syringes and scalpels) are sterilised using

⁵⁰http://gco.iarc.fr/today/online-analysis-pie?mode=cancer&mode_population=continents&population=990&sex=0&cancer=29&type=1&statistic=0&prevalence=0&color_palette=default

⁵¹ Radiotherapy equipment and departments in European countries: Final results from the ESTRO-HERO survey. Radiotherapy and Oncology 112 (2014).

⁵² “Additive” manufacturing.

ionising radiation devices⁵³. Sealed sources are mainly used for sterilization purposes. The encapsulation of electronics into packaging or medical materials increases the demand for safe and reliable sterilisation technologies that guarantee the required reduction in bio-burden pathogens. Only very low-energy electrons with a precisely-adjusted penetration depth can be used for product sterilization without destroying the sensitive electronics inside or degrading basic layers of composite materials. The sterilization of food is developing: China has completed a large electron-beam facility along its southern border in Pinxiang designed for phytosanitary import purposes that is capable of irradiating 100,000 tons of fruit per year. A European player in aseptic-carton packaging of liquid foods is currently installing e-beam sterilisation machines in its production facilities.

In environmental applications...

Poland has built a full-scale electron-beam accelerator facility to treat flue gases from coal-driven power plants, leading to a significant reduction in emissions of sulphur dioxide (SO₂), nitrogen oxides (NO_x) and polycyclic aromatic hydrocarbons. Traditional technologies using various chemical and physical processes have a similar efficiency in removing both NO_x and SO₂ pollutants, but require the construction of separate installations, consume large amounts of water, use toxic, metal-doped catalysts and produce a significant amount of radioactive waste⁵⁴. Ionizing radiation can be used for water purification and disinfection treatments, for decontaminating sewage sludge for reutilization in agriculture or for environmental remediation of hydrocarbon-contaminated soils.

The EU is at the forefront for fundamental and applied research...

In the fundamental-research field where ionizing-radiation technologies are used, Europe is at the forefront, with a series of world-class research infrastructures, equipment, labs and researchers. The areas of research are multiple.

Photon sources are used for:

- Chemistry, including areas of interest to industry such as catalysts and batteries;
- Biomedicine, including drug design and molecular biology relevant to health;
- materials science, including foods, polymers and textiles;
- nanotechnology, including nano-structured materials and nano-machines;
- condensed-matter physics, including studies of superconducting and magnetic materials relevant to electronics and information technology;
- environmental science, including atmospheric science, pollution and waste management;
- archaeology, including the imaging and study of ancient artefacts;
- industrial and manufacturing processes of all kinds;
- engineering including studies of aerospace materials.

⁵³ White paper: A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Industrial Sterilization of Medical Devices and Healthcare Products. AUGUST 31, 2017. Gamma Industry Processing Alliance (GIPA) and International Irradiation Association (IIA).

⁵⁴ <https://www.iaea.org/newscenter/news/scientific-forum-2015-electron-beams-help-polands-coal-driven-power-industry-clean-up-its-air>

In complement, neutrons sources are used:

- for imaging deep into solid objects to investigate their structure and strength, and to look at stresses that may impact the lifetimes of engineering components; examples include pipelines, turbine blades, train wheels and welds;
- in chemistry, to study chemical reactions of importance for the pharmaceutical, food and medical industries;
- in IT and computing, for materials studies to improve data storage and transmission;
- in magnetism, neutrons can probe complex magnetic structures and superconducting materials of significance to the electronics industry;
- in materials science, to determine the molecular structure of both crystals and disordered materials, including liquids and gases, for many applications, particularly in industry;
- in polymers and soft matter, to study the structure of polymers and to provide detailed dynamic studies of polymer films, and complex fluids such as cleaning materials, foods and personal-care products;
- in molecular biology and medical science, to study the arrangement of water molecules in biological systems, the structure of proteins and other large molecules relevant to disease, and even the behaviour of large biomolecular assemblies such as cell membranes, which may be significant in understanding the uptake of drugs by the body;
- in the environment, neutrons are employed in a wide variety of studies concerning pollution, climate change, agriculture and green energy;
- in cultural heritage: the non-destructive nature of neutron techniques (scattering and transmission) means they can be used to determine the composition and internal structure of antiquities and art objects.

Ionizing radiation applications have considerable impact on European economic growth, high level jobs and innovation ...

Assessing the economic impact of such diverse applications is difficult. Ionizing radiations tools and equipment are often embedded into products, services, manufacturing processes and researches in which their specific-added value cannot easily be computed. Nevertheless, it has been estimated that ionizing radiation applications of accelerators alone underpin nearly half-a-trillion-dollars' worth of commerce a year⁵⁵, without taking into account their invaluable health benefits.

The equipment portion of the ionizing-radiation equipment market is only a little less difficult to appraise. With this yardstick, the global market can be evaluated at more than EUR 25 bn, with Health applications being the most important non-energy domain using ionizing radiation (EUR 18.3 bn). The market is growing at 3-6%⁵⁶, driven largely by Asian markets. Competition in the equipment market is fierce with an increasing presence of US and Asian companies, relying upon strong domestic markets.

In Europe, over 1,000,000 workers are monitored by ESOREX⁵⁷ for their occupational exposure, of which more than 700,000 in the Health domain and about 90,000 in the

⁵⁵ Robert W. Hamm (R&M Technical Enterprises, Inc.) and Dr. R. Kephart, Director, Illinois Accelerator Research Center (IARC), Fermilab. Session TUIA2, IPAC17, Copenhagen Denmark.

⁵⁶ CAGR estimations given by diverse market analysts are often divergent.

⁵⁷ European Platform for Occupational Radiation Exposure.

non-nuclear energy industry (for 22 European countries). The major European medical-technology equipment manufacturers employ over 60,000 workers in Europe, a majority of whom have jobs in the IR field, and there are at least twice as many when considering the jobs induced along the supply chain.

As innovation is the key in this competitive market, large investments are required, triggering synergistic effects on many other technologies, including IA and big data, as well as fostering highly-skilled job opportunities and needs in Europe.

5. Economic impact of IR technologies

IR technologies result in tools which may be used per se (like scanning electron microscopes, for instance) but are most often incorporated into larger services, products or manufacturing processes, and may be mixed with other technologies, which makes challenging the appraisal of their market and of their specific added value.

Supplies	Example	Market Players
Components suppliers along the supply chain	Radiofrequency cavities for use in accelerators	OEM subcontractors, but also OEM Equipment manufacturer for some parts
Equipment supply	IR-Equipment itself	OEM Equipment manufacturers
Associated software supply	Software associated to the equipment allows to properly operate equipment, deliver treatment-decision support, store confidential patient data and medical information as well as exchange clinical knowledge, oversee patient-care management, support practice management and decision-making	
Equipment & Software Servicing contracts	Equipment Servicing, may comprise installation, warranty, repair, spare parts, software support, training and support services, project management, site planning, and other professional services.	OEM Equipment Manufacturers + non-OEM Equipment Servicing suppliers
Services, Products, Industrial Processes incorporating the IR-based equipment	Examples: - Cancer healing treatment administered in an hospital - Turnkey contracts for installations using the equipment (protontherapy unit turnkey contract including construction and project management - Services contracts using the equipment (sterilization contracts, border control system including operation, NDT field services) - Products, the manufacturing process of which uses the equipment (Electron-beam welding, e-beam melting, ion implantation on silicon wafers, etc.)	OEM Equipment manufacturers but mainly other products manufacturers and services suppliers

Table 3: IR-based tools, players and value chains in the market

The last market is the largest by far. Hence, given the various IR-tools uses, players and value chains in the market, it is specified which market is addressed when giving figures.

5.1. Health MedTech market

In the Health sector, ionizing radiation tools are used for diagnostics imaging, radiotherapy, nuclear medicine, dental applications and veterinary purposes.

5.1.1. Imaging diagnostic market

5.1.1.1. Characteristics of the equipment market

The Health ionizing-radiation equipment market considered here comprises three main components: hardware (supply of equipment), software and their associated servicing.

- Equipment supply (hardware) represents typically 40-45% of the market;
- Software typically represents 10 to 15% of the market and is used for various purposes: to properly operate equipment, deliver treatment-decision support, store confidential patient data and medical information as well as exchange clinical knowledge, oversee patient-care management, support practice management and decision-making;

- Equipment servicing is generally the recurrent part of the market players' revenues (typically 40%) via long-term contracts. These services comprise installation, warranty, repair, spare parts, software support, training and support services, project management, site planning, and other professional services.

5.1.1.2. Imaging diagnostics equipment market: status and trends

The global MedTech market in 2016 and its predicted evolution are given below⁵⁸.

**Worldwide Medtech Sales by EvaluateMedTech® Device Area:
Top 15 Categories & Total Market (2016 & 2022)**

Source: Evaluate, September 2017

Rank	Device Area	WW Sales (\$bn) 2016	2022	CAGR % Growth	WW Market Share 2016	2022	Chg. (+/-)	Rank Chg. (+/-)
1.	In Vitro Diagnostics (IVD)	49.4	69.6	+5.9%	12.8%	13.3%	+0.6pp	-
2.	Cardiology	44.6	62.3	+5.7%	11.5%	11.9%	+0.4pp	-
3.	Diagnostic Imaging	39.2	48.0	+3.4%	10.1%	9.2%	-1.0pp	-
4.	Orthopedics	35.0	44.4	+4.0%	9.0%	8.5%	-0.5pp	-
5.	Ophthalmics	26.0	35.4	+5.3%	6.7%	6.8%	+0.1pp	-
6.	General & Plastic Surgery	20.4	27.8	+5.3%	5.3%	5.3%	+0.0pp	-
7.	Endoscopy	17.8	25.7	+6.4%	4.6%	4.9%	+0.3pp	+1
8.	Drug Delivery	18.6	24.6	+4.8%	4.8%	4.7%	-0.1pp	-1
9.	Dental	12.8	17.8	+5.6%	3.3%	3.4%	+0.1pp	+1
10.	Wound Management	13.0	16.9	+4.5%	3.4%	3.2%	-0.1pp	-1
11.	Diabetic Care	11.0	16.2	+6.6%	2.9%	3.1%	+0.2pp	+1
12.	Nephrology	11.1	14.6	+4.6%	2.9%	2.8%	-0.1pp	-1
13.	General Hospital & Healthcare Supply	11.0	12.8	+2.5%	2.8%	2.4%	-0.4pp	-
14.	Neurology	7.4	11.6	+7.8%	1.9%	2.2%	+0.3pp	+3
15.	Ear, Nose & Throat (ENT)	8.0	11.1	+5.5%	2.1%	2.1%	+0.0pp	-1
	Top 15	325.4	438.6	+5.1%	84.1%	84.0%	-0.1pp	
	Other	61.4	83.3	+5.2%	15.9%	16.0%	+0.1pp	
	Total WW Medtech Sales	386.8	521.9	+5.1%	100.0%	100.0%		

Note: Analysis is based on the top 300 medtech companies. Sales in 2016 based on company reported data. Sales forecasts to 2022 based on a consensus of leading equity analysts' estimates for segmental sales.

Figure 4: MedTech Sales - SourceEvaluateMedTech® World Preview 2016, Outlook to 2022.

According to MedTech Europe⁵⁹, the European market represents about EUR 100 bn, i.e. about 30% of the US\$ 387 bn (about EUR 329 bn) global market.

The main players in the global Health MedTech field are:

Worldwide Medtech Sales: Top 10 Companies (2022)

Source: Evaluate, September 2017

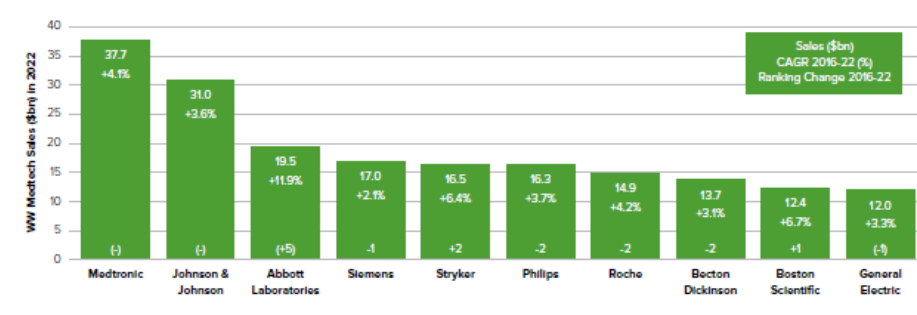


Figure 5 : Main players in the MedTech global market (same source)

Only a few of the MedTech areas depicted above include radiation-technology applications, namely Diagnostic Imaging and, to a far lesser extent, In Vitro Diagnostics (IVD)⁶⁰.

⁵⁸ These figures cover MedTech equipment and do not include the pharmaceutical field.

⁵⁹ MedTech Europe: European Medical Technology in figures.

The different types of Diagnostics Imaging equipment are:

- Non-IR-based tools: Magnetic Resonance imaging and Ultrasounds,
- And IR-based tools,
 - Computed Tomography,
 - Radiology, Fluoroscopy, Mammography, Urology,
 - Angiography
 - C-Arms for interventional radiology
 - Molecular imaging equipment (SPECT and PET, whereas Radioisotopes and Cold kits are accounted for separately).

The global Diagnostics Imaging market is dominated by 3 players, Siemens Healthineers, GE Healthcare and Philips with a market share of 65 to 70%⁶¹. Out of the US\$ 39.2 bn (EUR 33.3 bn⁶²) global market, EUR 20 bn are Equipment and Software sales, the remaining being Services⁶³. The EMEA part of the equipment market is about EUR 5.2 bn⁶⁴ of which EUR 3.5 bn (68%) in Europe⁶⁵, including Ultrasound and MRI. When considering only ionizing radiation-based equipment, Ultrasound and MRI must be excluded. The resulting IR-based Imaging Equipment global market then amounts to EUR 10.5 bn and the European one to EUR 1.8 bn⁶⁶. This concerns only the equipment and software sales. The Services business supports the equipment offering and targets the growing, highly fragmented, value-added services market, which is estimated to grow at a CAGR of 7-8% from 2016 to 2021. If services are considered (40%), the market totals EUR 10.5 bn / 60% = EUR 17.5 bn. The services market fraction in Europe is not known but is probably higher than 40% given the ageing of the equipment (see further in this report). Hence, the total Diagnostics imaging market in Europe comprising services amounts to at least EUR 1.8 bn / 60% = EUR 3 bn.

⁶⁰ IVD for a negligible share.

⁶¹ Siemens Healthineers Public Offering Document (5/3/2018).

⁶² With an assumed 0.85 €/€ exchange rate.

⁶³ Estimate based on main players' revenues (Siemens, GE Healthcare, Philips).

⁶⁴ Siemens Healthineers Public Offering Document (5/3/2018).

⁶⁵ COCIR Self-regulatory initiative for Medical Imaging Equipment 2016. See also appendix 21.

⁶⁶ Note: equipment + software, without equipment services (40% of the total sales).

2016 Market data		US\$ bn	EUR bn (iv)	Source	Main Market Players
Global Health Medtech Market		386,8		(1)	Siemens, GE Healthcare, Philips : > 2/3 of the market (excl Ultrasound) Other smaller players : Canon Medical (ex-Toshiba Medical), Hitachi, TeraRecon, Agfa Healthcare, Esaote, Neusoft, Hologic, Aloka, Analogic, Mindray, United Imaging, Samsung,... and Shimadzu, Medtronic, Ziehm Imaging
of which Global Diagnostics Imaging		39,2	33,3		
of which Services			13,3		
of which Equipment + Software by product			20,0	(2)	
	Ultrasound		5,3		
	Magnetic Resonance		4,2		
	Computed Tomography		3,4		
	RFMU (i)		3,4		
	Angiography		2,0		
	C-Arms		0,7		
	Molecular imaging		1,0		
of which Equipment + Software by geographic zone			20,0	(3)	
	Americas		6,8		
	Asia-Pacific		8,2		
	EMEA of which		5,2		
	Europe		3,5		
	Ultrasound		0,90		
	Magnetic resonance		0,80		
	Computed Tomography		0,46		
	X-Ray		1,14		
	Nuclear medicine		0,21		

Sources: (1) MedTech Sales - EvaluateMedTech® World Preview 2017, (2) Siemens Healthineers Public Offering Document (5/3/2018), (3) COCIR: Self-regulatory initiative for Medical Imaging Equipment 2016

Table 4: Diagnostics Imaging Market

A compound annual growth rate (CAGR) of 3% is anticipated from 2016 to 2021, with Asia-Pacific being the largest and fastest growing geographical region with a CAGR of 5% over the same period⁶⁷. The Imaging market is benefiting from a paradigm shift towards "Precision Medicine"⁶⁸ and an increasing utilization of imaging devices in therapy, screening and intervention. These trends will continue to drive the demand for broader imaging applicability and digitalization. Furthermore, just as developments in Artificial Intelligence, big data and deep-machine learning continue to direct the future of population-health management, highly-intelligent imaging systems will continue to become critical to the management and delivery of care. Growth in the market is also driven by broad macroeconomic trends in global healthcare, including ageing-population demographics and increasing healthcare expenditure in emerging markets.

More specifically, market trends are as follows:

- Developed markets are poised for imaging-system replacements: the installed base of imaging-equipment systems across developed markets, such as the United States and Europe, is ageing and some customers have extended the useful life on products for 10 years or longer. In Europe, the healthcare market had been stagnant for several years following the financial-debt crisis, which prompted budget cuts and uncertainty about future healthcare budgets. However, in the US CT-scanner market, for example, newly-established regulations such as NEMA Standard XR-29 safety rules⁶⁹, which became effective in 2016, require more rigorous radiation-dose reporting and monitoring. Such reporting and

⁶⁷ Siemens Healthineers Public Offering Document (5/3/2018)

⁶⁸ Precision medicine is a medical model that proposes the customization of healthcare, with medical decisions, treatments, practices, or products being tailored to the individual patient

⁶⁹ also known as MITA SmartDose Standard

monitoring obligations lead to increasing demand for next-generation CT scanners with lower radiation doses.

- An increased demand for improved imaging equipment in emerging markets like China, India, Brazil, the Middle East and Africa.
- Imaging software and data integration are driving the digitalization of healthcare and increased demand for digital and portable devices.
- An increased focus on precision medicine has been prompted by the use of hybrid modalities: e.g., PET in combination with other imaging modalities, primarily CT.

5.1.2. Radiotherapy Market: Status and trends

This market is mainly devoted to Oncology. The different types of equipment are largely:

- External radiotherapy (external beams of X-Rays or gamma-rays): intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), volumetric modulated-arc therapy (VMAT), Stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT);
- Brachytherapy, involving the insertion of radioactive seeds, wires or ribbons directly into a tumour or body cavity near the tumour;
- The emerging Protontherapy, which is another form of external therapy, as well as other developing ion therapies.

As is true of the Diagnostics Imaging market, Services account for a large share of the market (about 40%).

2016 Market data	US\$ bn	EUR bn (iv)	Source	Main Market Players
Global Radiation Oncology market	5,0	4,3	(4)	Varian Medical Systems, Elekta (90% of the X-Ray & Brachy market), Accuray, ...
of which External X-Ray and Brachytherapy	4,6	3,9		Soft : Philips, RaySearch Labs, BainLab
of which Services		1,6		
of which Equipment		2,3		
of which Protontherapy & al.	0,4	0,3		Varian, IBA, Hitachi

Source (4): Varian Medical Systems 2017 Annual Report, Elekta Annual Reports and <http://www.micromarketmonitor.com/market-report/radiotherapy-devices-reports-3833541330.html>

Table 5: Radiotherapy market

The global market (services included) can be valued at about US\$ 5 bn⁷⁰ (EUR 4.3 bn). Major players, sharing 90% of the market, are Varian Medical Systems (USA) and Elekta (Sweden). For the same reasons as for imaging, this market is growing at comparable CAGRs. EMEA fraction of the major players revenues are 32% and 28% respectively for Elekta and Varian. Assuming that the European market represents at least 80% of the EMEA market, the European market (services included) would amount at least to EUR 4.3 bn x 80% x 30% = EUR 1 bn.

The proton-therapy fraction of the market presents notable peculiarities. Although proton therapy has been in clinical use since the 50's, the major growth of proton therapy occurred at the beginning of the 21st century and the market is still developing. Proton-

⁷⁰ Varian Medical Systems 2017 Annual Report

therapy facilities are large-scale construction projects that involve significant customer investment (the cost of a proton-therapy centre project can range from a few tens of millions of dollars to over US\$ 100 million⁷¹) and often calls on complex project financing in which vendors must participate. Consequently, this business is vulnerable to general economic and market conditions, as well as repayment interest rates. Customer decision-making cycles tend to be very long ones, and orders generally entail many contingencies. While credit markets have improved in recent years, the funding environment for large capital projects, such as proton-therapy projects, remains constrained. However, market leaders like IBA (Belgium), Varian Medical Systems (USA) or Hitachi (Japan) anticipate strong development in Protontherapy in the short term.

As Protontherapy projects may, in whole or in part, involve project management, civil-engineering works, real-estate, equipment, commissioning as well as financing costs, and may extend over two years or more, evaluating the market's value reliably is particularly difficult for this emerging technology. Market shares depend on whether one is considering centres, treatment rooms or equipment, as shown below⁷²:

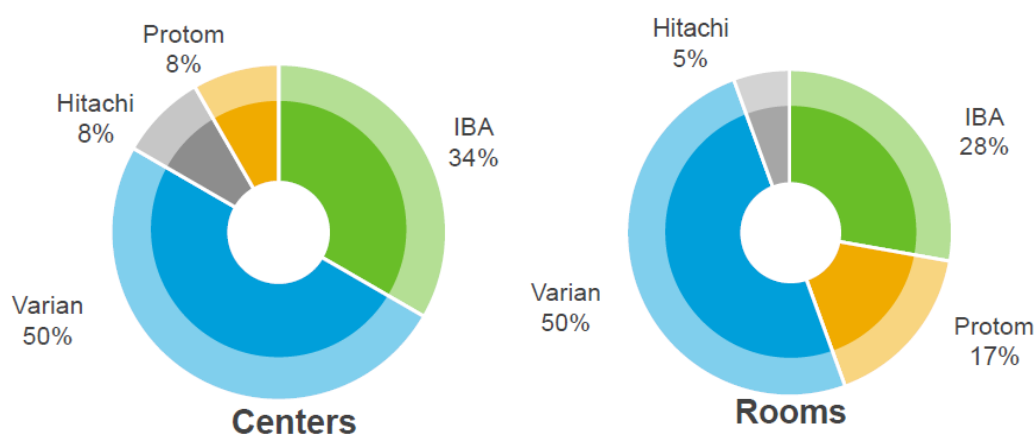


Figure 6: 2017 Market Shares Protontherapy⁷³

Other emerging technologies

BNCT (Boron Neutron Capture Therapy) is a therapeutic modality used to irradiate tumour cells previously loaded with the stable isotope ^{10}B , with thermal or epithermal neutrons, producing a $^{10}\text{B} (n, \alpha)^7\text{Li}$ reaction, whereby the reaction products deliver their energy within the tumour. This technique is capable of delivering a high dose to the tumour cells while the healthy surrounding tissues receive a much lower dose depending on the ^{10}B bio distribution. Recognised for a long time now, the development of this modality has long been hampered by the infrastructure necessary to produce the neutron beam (research reactor). Development projects currently exist for accelerator-based BNCT in Russia, the UK, Italy, Japan, Israel and Argentina⁷⁴. However, for the time being, the market remains negligible as compared to that for other modalities.

Very high energy electrons (VHEE) in the range from 100–250 MeV have the potential of becoming an alternative modality used in radiotherapy because of their improved dosimetry properties compared with MV (megavolt) photons from contemporary medical

⁷¹ Depending on the number of gantries, or the need for new buildings, etc.

⁷² IBA 2017 Full Year Results. 22/3/2018.

⁷³ IBA 2017 Full Year Results. 22 March 2018.

⁷⁴ Present status of Accelerator-Based BNCT. Reports of Practical Oncology and Radiotherapy 21 (2016).

linear accelerators, especially for treating deep-seated tumours. However, technological problems and conformal dose-delivery questions remain to be solved. The laser-plasma accelerator is a very recent ultra-compact technology that is now attracting the attention of the scientific community. By focussing high-intensity laser beams into plasma, scientists have demonstrated laser-plasma accelerators having accelerating gradients in excess of 1 GeV/cm, which is one thousand times greater than is possible in conventional accelerators. Hundreds of MeV electrons can be produced in a few millimetres. The laser-plasma accelerator dramatically reduces the size and costs of accelerator technology. However, for the time being, the VHEE market remains negligible compared to the other radiotherapy modalities.

5.1.3. Nuclear medicine: radioisotopes and cold kits

The practice of nuclear medicine requires equipment (SPECT or PET cameras and systems) calling on sophisticated software and services, as is true of CT, radiology or radiotherapy equipment. It also requires the products to be injected into the patient: a compound containing an imaging or therapeutic radioisotope and an associated vector to target the part of the body to be imaged or healed (the “cold kit”).

The supply chain for these compounds is complex, with numerous intermediary players. The compounds may be supplied to end-users⁷⁵ via centralised radiopharmacies in dose-ready form (in US or Japan practices, or in Spain in Europe), or as separate products, possibly shipped from separate suppliers (generators, cold kits) that a radiopharmacist prepares on demand in the hospital (general case in Europe). Hence, the main market suppliers may have different business models according to the particularities of each country. Each case being different, the revenues of market intermediaries must be restated in order to appraise the global market. When the intermediaries are excluded, Cardinal Health, GE Healthcare, Triad (Jubilant), UPPI in the US, Curium (for its direct sales to end-users) in Europe, Nihon and Fuji in Japan, and Bayer for radiotherapeutics, can be identified as the current main players in the market among over 50 other players.

The NM compounds are either imaging compounds or therapeutic agents. Suitable to specific organs and illnesses, some 100 products are marketed, while over 100 others are being investigated. In value, the main products marketed are Mo-99/Tc-99m generators, Tc-99m doses ready to use, cold kits, and supporting equipment⁷⁶. The 2016 market was estimated at US\$ 4.5 bn (EUR 3.8 bn)⁷⁷.

2016 Market data	US\$ bn	EUR bn (iv)	Source	Main Market Players
Radioisotopes & Cold Kits for Imaging & Therapy Global Market (ii)	4,5	3,8	(7)	Cardinal Health, GE Healthcare, Curium, Jubilant (Triad), Nihon Medi-Physics, Fujifilm RI Pharma, Siemens/PETNET, and >> 50 smaller players

Source (7): MedRaysIntell. Nuclear Medicine World Market Report 2017

Table 6: Nuclear medicine market

⁷⁵ The end-user is defined here as being the hospital or the care centre administering the compound to the patient.

⁷⁶ A typical generator (50 doses) is sold EUR 1000 in Europe. Tc-99m doses ready-to-use are sold above US\$ 100 in the USA. Typical PET ready-to-use dose selling price is EUR 200 in Europe. Cold kits may represent 30% of the SPECT/PET products sales. These figures are largely dependent upon the country, the business model, the type of contracts, whether the product is patented or generic, etc...

⁷⁷ MedRaysIntell Market Study 2016.

Whereas the imaging-compounds market is rather stable at the moment, this is not the case of the therapeutic-compounds market, where the first radiopharmaceutical “key growth product”⁷⁸ only appeared on the market a few years ago. Other products are taking off⁷⁹, showing promising results.

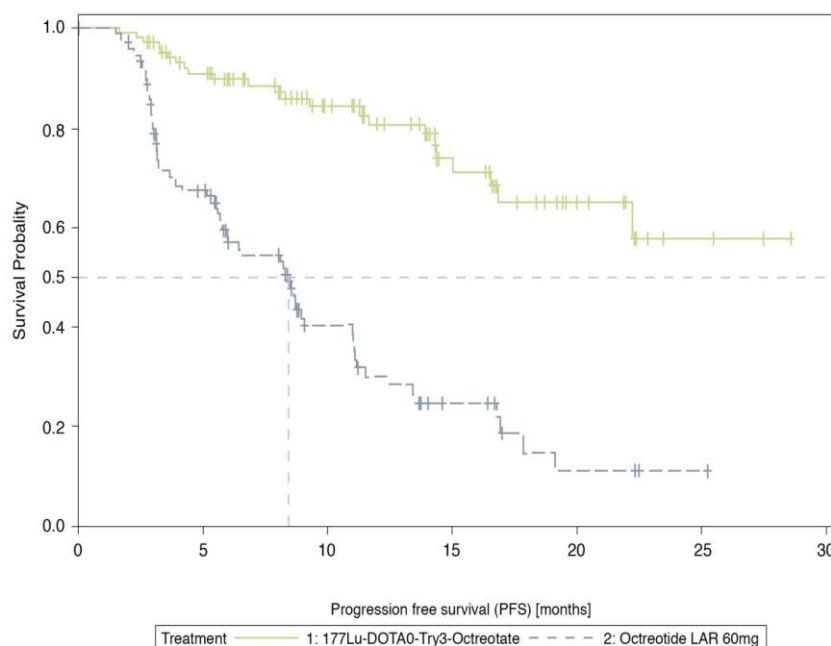


Figure 7 : Lu-177 Dotatate Netter-1 trials results⁸⁰

Major pharmaceutical companies enter the game, attesting the development potential of radiotherapeutics. These factors and the projected selling-price levels of the new radiotherapeutics⁸¹ give strong credit to the predictions of market analysts⁸² anticipating a bright future for theranostics.

⁷⁸ Pharmaceutical companies use this term for their most promising or best selling drugs. Bayer’s Xofigo® (a pain palliative radiopharmaceutical) sales amounted to EUR 408 m in 2017, just 4 years after European and US market approvals.

⁷⁹ Luthatera® just got its FDA approval. Other Lu-177-based radiopharmaceuticals are being actively developed; other companies are developing α -emitter 225Ac-based radiopharmaceuticals, etc.

⁸⁰ 177Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumours: Results of the Phase III NETTER-1 Trial. Jonathan Strosberg, Edward Wolin, Beth Chasen, Matthew Kulke, David Bushnell, Martyn Caplin, Richard P. Baum, Erik Mittra, Timothy Hobday, Andrew Hendifar, Kjell Oberg, Maribel Lopera Sierra, Philippe Ruszniewski, Dik Kwekkeboom, on behalf of the NETTER-1 study group

⁸¹ <https://www.reuters.com/article/us-advanced-accelerator-fda/fda-clears-radioactive-drug-for-cancer-that-killed-steve-jobs-idUSKBN1FF29K>. Luthatera® has obtained outstanding results in terms of survival for NET cancers according to the NETTER 1 trials. A list price of US\$ 47 500 per dose of Lu-177 based Lutathera® before potential rebates offered by drugmakers (4 doses necessary) has been announced. Given a potential of 27,000 US patients, this would mean, for this sole drug, a market of more than US\$ 5 bn for Novartis, which bought the AAA European developer for about US\$ 4 bn at the end of 2017.

⁸² Richard Zimmermann, 11/5/2017 Presentation in Mechelen.

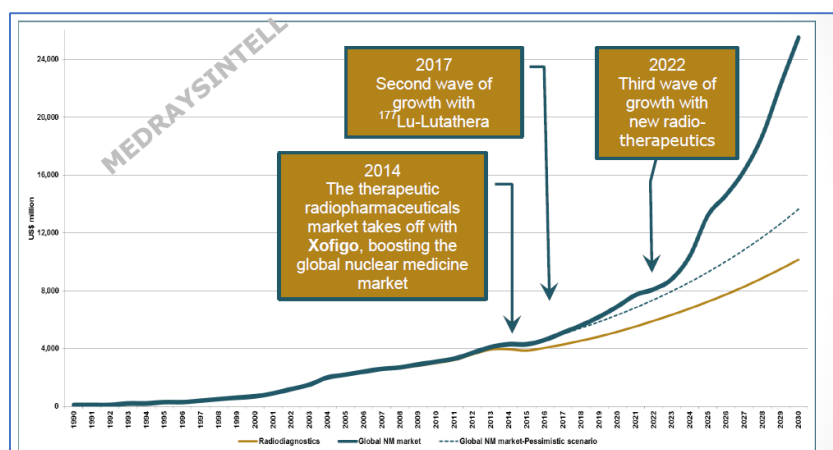


Figure 8: Possible market evolution for radiotherapeutics – source MedRaysIntell (2016)

Defining reliably the European fraction of the market is impossible. Given the different business models in USA and in Europe, such an evaluation would require that the activities of the US centralised radiopharmacies players are removed from the total or that the activities of the European hospitals-integrated radiopharmacies are considered as a separate “business”, which does not make sense. A very rough yardstick could be the relative fractions of Mo-99 procedures, which represent at the moment the largest fraction of the imaging procedures. The world distribution of these procedures is roughly 55% (USA), 25% (Europe) and 20% (rest of the world). With this very rough yardstick, the EUR 3.8 bn European share of the global market would be around $\text{EUR } 3.8 \times 25\% = \text{EUR } 1 \text{ bn}$. It must be stressed that this figure cannot be analytically justified and does not take into account the anticipated development of radiotherapeutics.

5.1.4. Other applications

Other applications concern the Dental and the Veterinary sectors.

2016 Market data	US\$ bn	EUR bn (iv)	Source
Global Dental X-Ray (2015)	1,8	1,5	(5)
Global Veterinary imaging market (2017)	1,4	1,2	(6)

Sources: (5) <https://www.grandviewresearch.com/industry-analysis/dental-x-ray-market>,
(6) <https://www.marketsandmarkets.com/Market-Reports/veterinary-imaging-market-80889726.html>

Table 7: Other Health markets

5.1.5. Conclusion: Ionizing radiation based medical-equipment market

The total value of the market, when adding Diagnostics-imaging equipment + software (all modalities, with services) to Radiation-oncology equipment, Dental and Veterinary equipment, and radioisotopes, amounts to EUR 44.3 bn; it is growing at an attractive pace, with a sharp increase in the radiotherapeutics market being forecast. When accounting for the IR-based equipment + software alone, including equipment and software servicing, the global market comes to about EUR 28.3 bn.

Table 8: Ionizing radiation equipment in the MedTech market (2016)

2016 Market data	US\$ bn	EUR bn (iv)	Source	Main Market Players
Global Health Medtech Market	386,8		(1)	
of which Global Diagnostics Imaging	39,2	33,3		
of which Services		13,3	40%	
of which Equipment + Software by product		20,0		
Ultrasound		5,3		Siemens, GE Healthcare, Philips : > 2/3 of the market (excl Ultrasound)
Magnetic Resonance		4,2		
Computed Tomography		3,4		
RFMU (i)		3,4		
Angiography		2,0		
C-Arms		0,7		
Molecular imaging		1,0		
of which Equipment + Software by geographic zone		20,0		
Americas		6,8		Other smaller players : Canon Medical (ex-Toshiba Medical), Hitachi, TeraRecon, Agfa Healthcare, Esaote, Neusoft, Hologic, Aloka, Analogic, Mindray, United Imaging, Samsung,...
Asia-Pacific		8,2		
EMEA of which		5,2		
Europe		3,5		and Shimadzu, Medtronic, Ziehm Imaging
Ultrasound		0,90		
Magnetic resonance		0,80		
Computed Tomography		0,46		
X-Ray		1,14		
Nuclear medicine		0,21		
Global Radiation Oncology market	5,0	4,3		
of which External X-Ray and Brachytherapy	4,6	3,9		Varian Medical Systems, Elekta (90% of the X-Ray & Brachy market), Accuray, ... Soft : Philips, RaySearch Labs, BainLab
of which Services		1,6		
of which Equipment		2,3		
of which Protontherapy & al.	0,4	0,3		Varian, IBA, Hitachi
Global Dental X-Ray (2015)	1,8	1,5	(5)	
Global Veterinary imaging market (2017)	1,4	1,2	(6)	
Radioisotopes & Cold Kits for Imaging & Therapy Global Market (ii)	4,5	3,8	(7)	Cardinal Health, GE Healthcare, Curium, Jubilant (Triad), Nihon Medi-Physics, Fujifilm RI Pharma, Siemens/PETNET, and >> 50 smaller players
Medtech Equipment + Services Global market 2016	44,1			
Ionizing Radiation Equipment Global Market 2016 (Equipment + software+equpt servicing)	28,3		64%	

Sources

- (1) MedTech Sales - EvaluateMedTech® World Preview 2017
- (2) Siemens Healthineers Public Offering Document (5/3/2018)
- (3) COCIR : Self-regulatory initiative for Medical Imaging Equipment 2016
- (4) Varian Medical Systems 2017 Annual Report, Elekta Annual Reports and <http://www.micromarketmonitor.com/market-report/radiotherapy-devices-reports-3833541330.html>
- (5) <https://www.grandviewresearch.com/industry-analysis/dental-x-ray-market>
- (6) <https://www.marketsandmarkets.com/Market-Reports/veterinary-imaging-market-80889726.html>
- (7) MedRaysIntell. Nuclear Medicine World Market Report 2017

Notes

- (i) RFMU : Radiography, Fluoroscopy, Mammography, Urology
- (ii) Market at end-user level (for SPECT : doses in USA, Japan, Spain, and generators in Europe. For PET : doses ...)
- (iii) Equipment +Software + servicing, Ultrasound & MRI removed, Dental & veterinary assumed fully ionizing radiation based, removal of intermediates in RI supply chain
Assumption 0,85 €/US\$

In conclusion, the MedTech world market is estimated at about US\$ 387 bn (about EUR 329 bn), of which the European market (about EUR 100 bn) accounts for over 30%. For Health Imaging and Therapy applications, all modalities and services included), the global market represents about EUR 44.1 bn. The ionizing radiation-based equipment global market is estimated at EUR 28.3 bn (64%). The European radiation-technologies equipment market tends to be based on replacements and upgrades, due to an

increasingly cost-sensitive maturity factor. Thus, the equipment servicing part of this market is probably higher than 40%; assuming that the European market represents at least 18% of the market (3.5/20.0), the European ionizing radiation equipment market (equipment + software + servicing) value is certainly higher than EUR 28,3 bn x 18% = EUR 5 bn.

The anticipated growth of the global equipment market stems mainly from emerging countries and highlights the strategic importance of the Ionizing radiation-based equipment market to the EU trade balance.

5.2. Industry market

5.2.1. Evaluating the market: a real challenge

There is a wide variety of applications for radiation technologies in industry:

- Industrial radiography and imaging (X-Rays, γ -Rays, neutrons) for non-destructive testing and examinations, as well as for security applications;
- Irradiation for material processing, new-materials development, electron-beam welding, ion implantation, additive manufacturing, Neutrons-transmutation doping, etc.;
- Irradiation for sterilization (health equipment, food, etc.);
- Radiotracers applications;
- And all types of examinations at the atomic, molecular and mesoscopic scales used in industry and in research fields.

Contrarily to the Healthcare field, which is relatively concentrated with a few major companies dominating the market, estimating the magnitude of the industrial-equipment market is a real challenge because the industrial market includes tens of applications, thousands of players, ranging from small companies (sales of just a few million euros) to large worldwide conglomerates marketing thousands of machines/equipment and services.

The players are:

- components manufacturers, equipment manufacturers, systems manufacturers, often operating within complex supply chains, offering not only components, equipment or systems servicing (maintenance, spare parts, revamping, software support, etc.), but also project management or financing services for the most complex systems;
- companies integrating the diverse IR-based tools, ranging from portable equipment up to large installations, into more global service contracts such as sterilization contracts, or turnkey security screening solutions, comprising the construction, staffing and long-term operation of security screening checkpoints, for instance;
- companies in various industrial fields, using in-house IR equipment as part of their manufacturing process, among many other types of industrial equipment (e.g. a carton-packaging company sterilizing its carton packages, or mechanical manufacturers in the industry using e-Beam welding machines, etc.);
- and companies mixing these 3 business models.

When reliable public-domain business figures are available for all these companies, isolating the specific added value generated by radiation-based equipment is most often impossible. Hence, the least disputable market yardstick is the equipment value, including its equipment servicing component. But even this equipment value could not be assessed in several cases.

This explains why, within the framework of this study, only orders of magnitude are given regarding the IR-based industry market.

The equipment market can be segmented by the nature of radiation emission (charged particles-Beams, X-Rays and most often gamma-emitters radioisotopes) and by industrial use: sterilization & disinfection, processing, characterization and environmental applications.

Modality	Sterilization	Material processing	Detection, Imaging, NDT, Border control/security	Environmental applications	Nr of equipment in use	Equipment market (US\$ mn)
E-Beams Material processing & studies	Seed treatment, Disinfection of grains, nuts and spices Medical devices sterilization Food irradiation	Cutting, linking and pasting at the molecular level : 2D printing (food packaging) Heating and local surface modification and drilling, 3D printing, Lacquering and coating, Grafting Heating and local surface modification and drilling : melting, evaporation, welding, joining, drilling, hardening, diffusion, sintering, ... Example : Electron Beam Welding, Additive Manufacturing	Analytical methods using electrons (scanning electron microscopy, transmission electron microscopy, Auger electron spectroscopy, X-ray photoelectron spectroscopy and computer-aided tomography)	Flue-gas treatment, Treatment of waste-water and sewage, Environmental remediation of hydrocarbon contaminated soils, Conversion of fossil fuels, Asphalt treatment	10500 (without detection)	500
		Cross linking of materials (largest application) : Wire & cable insulation – heat resistant, Heat shrink tubing, Heat shrinkable food packaging films, Closed cell polyethylene foams – auto & medical parts, Tire components, Curing of inks, coatings & adhesives – paper, wood, metals & plastics, Hydrogels for wound dressings Semiconductor modification Colouring gemstones				
Ion beams		Ion Implantation : Semiconductor industry (largest application) Metals : Harden cutting tools, Reduce friction in metal parts, Biomaterials for implants, Ceramics & Glasses : Harden surfaces, Modify optics. Proton-beam writing, Nanomaterials, Polymers	Ion beam analysis › Elastic or Rutherford backscattering (EBS or RBS), and also nuclear reaction analysis (NRA); › Particle-induced X-ray emission (PIXE), with an X-ray detector; › Particle-induced gamma-ray emission (PIGE), with a gamma detector; › Elastic recoil detection analysis (ERDA) with a particle detector at a forward recoil/scattering angle used in ENVIRONMENT (Air pollution) and CULTURAL HERITAGE labs		11000 ion implantation 300 ion beam analysis	1600 (ion implantation) 50 ion beam analysis
Synchrotron		Analysis Techniques : Fourier Transform infra-red spectroscopy, Infrared microscopy, Circular dichroism, UV-VUV photo-electron spectroscopy (ESCA), VUV-microspectroscopy, Powder & surface diffraction, Small angle & wide angle X-ray scattering			70 emerging technology	

Modality	Sterilization	Material processing	Detection, Imaging, NDT, Border control/security	Environmental applications	Nr of equipment in use	Equipment market (US\$ mn)
X-Rays	Medical devices sterilization		Material studies : see E-Beams above Non-destructive testing Border control security :		2000 High Energy Border control/Security : several thousands, unknown	
	Medical devices sterilization Gamma : main market share among EO+Radiation+Steam for single use medical devices sterilization		Industrial Gammaography: The global gamma radioactive sources market for NDT applications is segmented mainly by sources into Iridium-192, Selenium-75, and Cobalt-60 Gauging applications (Well logging/moisture gauges, Level, Density, thickness gauges). Instrument calibration sources.	Conversion of fossil fuels	200 large installations operating in the world + in-house installations of med devices manufacturers	see remarks below
Neutrons		Silicon doping	- Thermal neutron capture : Cf-252 sources - (fast) Neutron inelastic scattering : Am-Be-241 sources.. NIS used for on-line and on-belt controls in cement, mineral & coal industries, water analysis in bore holes. - Neutron activation analysis - Neutron imaging		2000	50
Equipment market	US\$ 4700 mn, but covers also reusable materials sterilization in hospitals (largest segment, non radiation-based), ... US\$ 2400 mn covers only sterilization services with Steam, EO, gamma & e-beam, but covers also hospitals and food & beverage Main players turnover (Radiation-based services part) : Steris : US\$ 440 mn, Sterigenics : US\$ 320 mn. Gamma-rays part of the market < US\$ 1 bn ?	Ion implantation (largest market) : US\$ 1600 mn. E-Beam machines : US\$ 340 mn Silicon doping : < 80 US\$ 80 mn (2014)	Equipment : - X-Ray : > US\$ 500 mn ? - Neutrons : US\$ 50 mn X-Based NDT Market : > US\$ 500 mn ? Border control & security services market radiation-based: unknown NAA & neutron imaging : < several US\$ mn		> 25000	> US\$ 2200 mn
Services Market				Emerging applications. Pilot plant existing in Poland, China, ...		

Figure 9: Industrial radiation-based applications (Beams and neutrons). Equipment market

From this table (sources are indicated in the next paragraphs), the industrial radiation-based equipment market can be valued at over US\$ 2.2 bn (EUR 1.9 bn) for the beam business alone⁸³, and services associated with this equipment represents much more.

The most important industrial applications in terms of equipment-market value are commented in greater details in the following paragraphs:

- the electron-beam business, pointing up the importance of the semiconductor industry: ion implantation and process control, and neutron transmutation doping;
- the sterilization/disinfection business;
- other radioisotopes applications
- Cargo screening and security applications
- Other neutron-based applications
- Consumer products

5.2.2. The beam business

The equipment market encompassing the beam business⁸⁴ (excluding Healthcare-related applications such as medical radioisotopes production machines or radiotherapy equipment), is detailed below.

Beam Business	US\$ mn
Commercial applications	
Ion Implantation - semiconductors and materials	1 600
Electron Beam Material Processing	180
Electron Beam Materials Irradiators	160
Developing Commercial Applications	
Neutron Generators	50
Non-destructive Testing & Inspection Linacs	160
Ion Beam Analysis	50
Synchrotron Radiation (?)	
Total	> 2 200

Table 9 : Accelerator market (equipment only) excluding Health equipment

More than 70 equipment vendors worldwide are in the accelerator business. Vendors are primarily in the US, Europe and Japan, although growing in China⁸⁵, Russia and India.

⁸³ Health applications excluded.

⁸⁴ “Industrial Accelerators” are defined here as all accelerators producing charged particle beams, except for the medical-therapy and physics-research sectors. This category does not include internal-beam devices (cathode ray tubes, X-ray tubes, RF tubes, electron microscopes or lithography systems). Specialized industrial accelerator applications are also excluded: neither focused ion beams (FIB) used in the semiconductor industry for the inspection and ablation of materials, nor Ion-beam figuring (IBF), a relatively new technique used in preparing optical and nano-material surfaces, are included. “Industrial accelerators” encompasses >50% of all accelerators now being sold.

⁸⁵ e.g.: see the impressive figures related to Radiation Science and Technology applications in China (ICARST 2017)

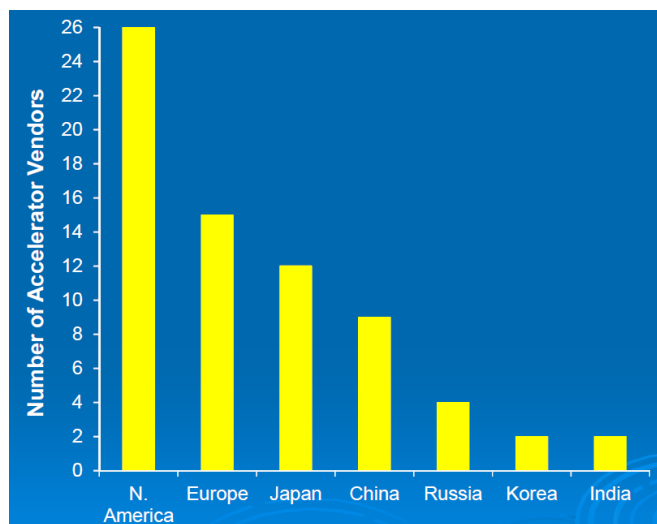


Figure 10: Accelerator vendors worldwide: 23 when adding Japan, China and Korea⁸⁶

Updated totals indicate that >25 000 systems⁸⁷ have been sold and an estimated >20 000 are still in operation today.

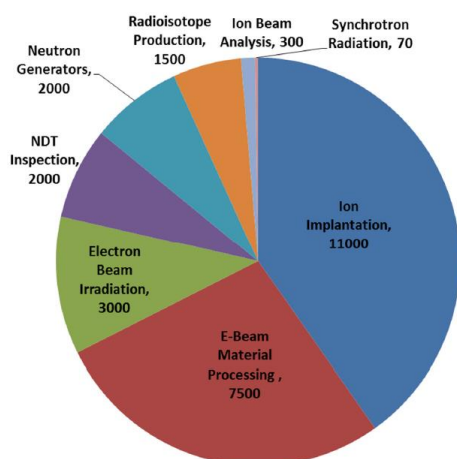


Figure 11: Number of accelerators in the world⁸⁸

Most of the machines are ion-implantation machines used in:

- The semiconductors industry (CMOS transistor manufacturing essentially for all IC devices, CCD & CMOS imagers for cell phones & digital cameras, and cleaving silicon for producing photovoltaic solar cells). This field is described more closely in the next paragraph.
- The metals-processing industry: hardening of cutting tools, reducing friction in metal parts, and biomaterials for implants;
- The ceramics and glasses industry: hardening surfaces or modifying optics.

E-beam material processing is critical to automotive production, for welding & hardening of parts or dissimilar metals and deep welds. It is also used for precision cutting and

⁸⁶ Ibid.

⁸⁷ Health applications are excluded.

⁸⁸ Industrial Accelerators. R.W.Hamm. IPAC-13. May 15, 2013. Shanghai, People's Republic of China.

drilling and recovering refractory metals. The typical industry sectors where it is used (besides MedTech) are in the automotive, machine-construction, and aerospace sectors. Additive manufacturing is a promising area for e-beams (see manufacturing examples, box below).

Additive manufacturing

Additive manufacturing (AM) calls on technologies that build 3D objects by adding layer-upon-layer of material, whether the material is plastic, metal, concrete or one-day-old human tissue. E-beam accelerators are currently being used for a technology known as e-beam melting (EBM), which enables producing metallic components having a high degree of complexity using computer-aided design (CAD) data. EBM is a powder-bed-fusion technology, by which high-density components are created by selectively melting this powder in a layer-by-layer fashion. In addition, a wire-based build-up welding technology is used, by which large-dimension components are created via the local build-up of structures by welding wire-fed material into layers. The forerunner for powder-based technology is Arcam in Sweden, which was recently bought by General Electric. The leading manufacturer for wire-based technology is Sciaky in the US.

Surface machining

Surface modification (SM), ranging from surface machining to structuring, is the umbrella term for all existing e-beam (EB) process variants that modify the surface properties of a component. These include hardening, re-melting, alloying, embedding and structuring. As for other applications, the most important advantage of EB-SM is that the desired modification can be achieved precisely in those specific areas where it is needed — while everything else remains 'spared'.

E-beam drilling

Mechanical drilling is often unsuitable (with regard to technical capability or economic viability) for producing ultra-fine holes, especially in high-strength materials. If a large number of holes have to be introduced into a component in a short period of time, the mechanical process cannot cope. E-beam processes offer much better solutions. E-beam perforation is already being used for many applications, including the paper industry, the food industry, fibre manufacturing (spinning plate for glass fibre production) and the aerospace industry.

Electron Beam Irradiator Applications are also used for:

- Cross-linking materials (largest application):
 - o Wire & cable insulation – heat resistant;
 - o Heat shrink tubing;
 - o Heat shrinkable food packaging films;
 - o Closed cell polyethylene foams – auto & medical parts;
 - o Tire components;
 - o Curing of inks, coatings & adhesives – paper, wood, metals & plastics;
 - o Hydrogels for wound dressing.
- Food and waste irradiation & sterilization (emerging applications).

High Energy X-Ray inspection applications include CT systems and are used for radiography of large castings, examination of rocket motors and munition, as well as examination of containers & semi-trailers in ports. Lower-energy applications such as X-Ray screening in airports and other public venues are not included in this category and are listed in a paragraph below.

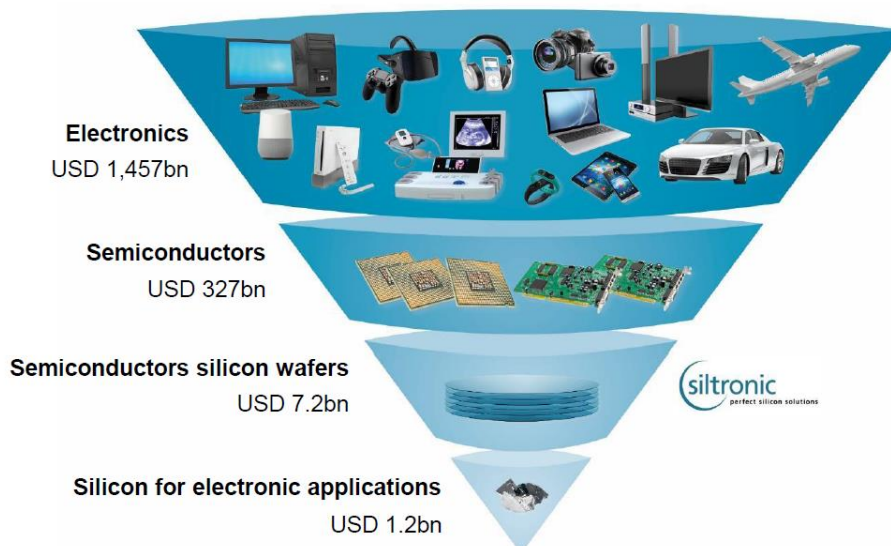
Ion-Beam Analysis applications encompass Rutherford Backscattering (RBS), Elastic-Recoil Detection Analysis (ERDA), Nuclear-Reaction Analysis (NRA), Particle-Induced X-ray Emission (PIXE), Particle-Induced Gamma Ray Emission (PIGE), Nuclear-Resonance Reaction Analysis (NRRA), Resonant-Scattering Analysis (RSA), Charged-Particle Activation Analysis (CPAA), Accelerator Mass Spectrometry (AMS), and are used largely in many research fields.

Finally, emerging synchrotron radiation applications are Fourier-Transform infra-red spectroscopy, Infrared microspectroscopy, Circular dichroism, UV-VUV photo-electron spectroscopy (ESCA), VUV-microspectroscopy, Powder & surface diffraction, Small angle & wide angle X-ray scattering (SAXS-WAXS), Protein Crystallography, Microtomography, X-ray fluorescence (XRF) and X-ray microscopy, X-ray absorption spectroscopy: EXAFS, XANES and fabrication techniques such as UV-VUV lithography (Microelectronics) and X-ray lithography (LiGA) for MEMS (sensors, gears, etc.). The applications under study concern the semiconductors industry (lithography, material-interface studies and production issues), the chemical industry (determining properties such as stress or texture of various manufactured materials and chemical reactions) and biomedical industry (protein crystallography, molecular-structure imaging, and molecular-dynamics studies in tissue cells)⁸⁹.

5.2.3. Applications in the semiconductor industry

The global electronics value chain is illustrated below.

Electronics value chain 2016



Source: Electronics (IC Insights), Semiconductors (WSTS, only silicon-based), Silicon wafers (SEMI SMG), electronic applications (WACKER estimate)



© Siltronic AG 2017

Figure 12: Electronics value chain 2016 - Siltronic

⁸⁹ See APAE-EUCARD Final Report, 2017

Ionizing-radiation tools are used at the semiconductors IC manufacturing level, using ion-implant equipment and process control, and also at the silicon-wafer production level (Neutron transmutation doping).

5.2.3.1. Ion-beam implantation & Process control

During the ion-implant process, wafers are bombarded by a beam of electrically-charged ions, called dopants, which change the electrical properties of the exposed semiconductor material. At the same time, checks of the integrated circuit are necessary at different stages of manufacturing and are currently performed largely by optical instruments. However, with miniaturization of transistors below the 10 nm process node⁹⁰, optical-control means may fall into that “grey area” where e-beam control may develop quickly. Simply put, electrons from an e-beam tool hit and penetrate the surface of a sample, followed by electrons scattering and bouncing back onto a detector in the tool. The secondary electrons or backscattered electrons are used to help identify defects in devices.

The market for ion-implant systems and materials-modification tools is evaluated at US\$ 1.5 bn⁹¹. In addition, there are substantial markets for suppliers of dopant-species materials (~US\$ 140 million/year) and a miscellaneous array of suppliers providing spare and upgrade parts as well as services. Additional players in the commercial infrastructure underpinning ion-implantation processes include suppliers of system components, of magnets, power supplies, and vacuum pumps, as well as an array of metrology tools devoted to process characterization and control applications.

The average number of commercial ion-implantation systems sold per year, predominantly for fabrication of silicon-based IC devices, has increased from ~250 to ~400 per year since 1980, as seen in the figure below. The year-to-year sales show large fluctuations due to the highly cyclical nature of IC manufacturing trends, especially when driven by additional factors, such as shifts in dominant wafer sizes, introduction of new implanter machine types and IC devices, expansion into new global regions, and variations driven by general economic cycles. The combination of these technology and market factors has resulted in a rather steady “5-year” cycle in units sold per year over the last 3 decades.

⁹⁰ The term “10 nm” (nanometer: one billionth of a meter) is a commercial name in the semiconductor industry for a generation of a particular size of wafers and its associated technology and does not express the dimensions of a transistor.

⁹¹ Ion implantation for Semiconductor devices: the major use of industrial accelerators; S.B. Felch, M.I. Current, M.C. Taylor. Proceedings of PAC2013, Pasadena, CA USA, from which these paragraphs are issued. and M.I. Current, “Ion Implantation for Fabrication of Semiconductor Devices and Materials,” in Industrial Accelerators and Their Applications, eds. R.W. Hamm, M.E. Hamm, World Scientific (2012), 9-56.

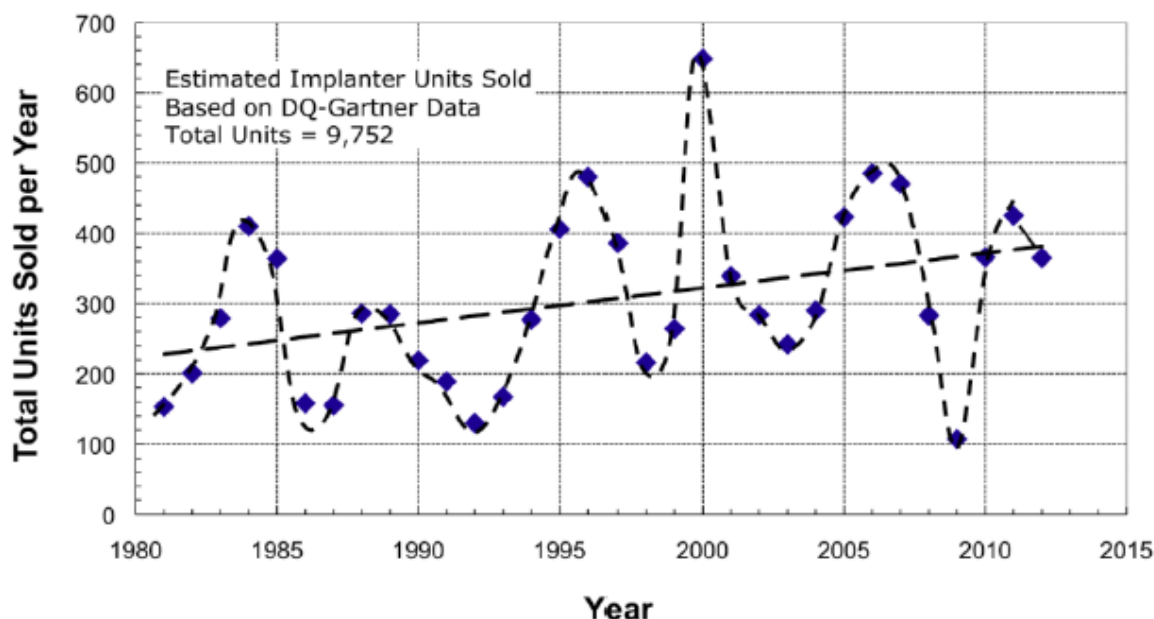


Figure 13 : Number of implant machines sold per year

In addition to ion implantation, the total patterned-wafer⁹² inspection market is expected to reach about US\$ 1.65 billion in 2018, up from US\$ 1.4 billion in 2017, according to Gartner⁹³. The figure includes both optical and e-beam techniques. Of that amount, “the e-beam inspection market was just under US\$ 200 million in 2016; it should be around US\$ 230 million in 2018.”

The main players in the market

Accelerator systems for ion implantation are provided commercially by a number of vendors, with the business being dominated by a few long-standing companies. Applied Materials/Varian Semiconductor Equipment (USA) is the market leader; Nissin Ion Equipment (Japan) has a strong Asian market position; Advanced Ion Beam Technology (Taiwan) is a new high-current vendor; Axcelis Technologies (USA) leads the high-energy market. SEN Corporation (Shikoku, Japan) is among the main players. Other smaller vendors exist, namely in Europe, like Ion Beam Services (France), an innovative new Plasma Immersion Ion Implantation (PIII) and SiC implanter company, or High Voltage Engineering (Netherlands), and several radio-frequency (RF) linear accelerators vendors.

In the process control and yield-management systems market, the main competitors are Applied Materials (USA), ASML Holding N.V. (Netherlands), Hitachi High-Technologies Corporation (Japan), Nanometrics, Inc. and Rudolph Technologies, Inc. (USA).

The customer base:

The customer base for all the above equipment is overwhelmingly Asian, as shown in the following table listing the market leader’s sales by country⁹⁴.

⁹² Patterned wafers have some circuitry partly drawn on them.

⁹³ <https://semiengineering.com/e-beam-inspection-makes-inroads/>

⁹⁴ Applied Materials Annual Report 2017.

Applied Materials 2017 Sales	US\$ mn	
Korea	4,052	28%
Taiwan	3,291	23%
China	2,746	19%
Japan	1,518	10%
Southeast Asia	640	4%
Asia Pacific	12,247	84%
United States	1,474	10%
Europe	816	6%
Total	14,537	100%

Table 10: Main Varian customers

Two customers alone account for 38% of the market leader's sales: Samsung Electronics Co., Ltd (Korea) with 23% of sales and Taiwan Semiconductor Manufacturing Company Limited (Taiwan), with 15%.

5.2.3.2. Neutron Transmutation Doping (NTD)

Historically, neutron fluxes stemming from research reactors have been used to dope silicon ingots, achieving an excellent homogeneity of the doping. Virtually all large research reactors have developed a NTD process: BR2 (Belgium), OSIRIS (France, now shut down), HFR Petten (NL), Hanaro (Korea), OPAL (Australia), Safari-1 (South Africa), FRM II (Germany), etc., or plan to do so in future, and aside from medical radioisotopes production, as is true of KJRR (Korea).

The 2016 global silicon-wafer market was valued at US\$ 7.2 bn⁹⁵. The leading four companies in the global silicon wafers market are SUMCO Corporation (Japan), Shin-Etsu Chemical Co., Ltd. (Japan), Siltronic AG (Germany), and LG Siltron Co., Ltd (Korea). Other key players in the market are Global Wafers Co. (Taiwan), Ltd., and Wafer Works Corporation (Taiwan). Okmetic (Finland) was acquired by a Chinese company in 2016⁹⁶.

In 2014, the global wafer market was valued at US\$ 7.6 bn⁹⁷, up in relation to 2016 due to the cyclical aspects of this market. According to Topsil, a Danish company that worked in this field until 2016⁹⁸, the power-electronics segment of this market represented some 10% (US\$ 790 million), with a 10% share of these 10% accounted for by NTD services (i.e. a global market of US\$ 78 million).

⁹⁵ Siltronic AG. Fact Book Investor Relations. October 2017.

⁹⁶ National Silicon Industry Group.

⁹⁷ <https://www.businesswire.com/news/home/20150624005546/en/Research-Markets-Silicon-Wafers-Semiconductor-Device-Processing>

⁹⁸ When the Topsil semiconductor business was sold to GlobalWafers (Taiwan).

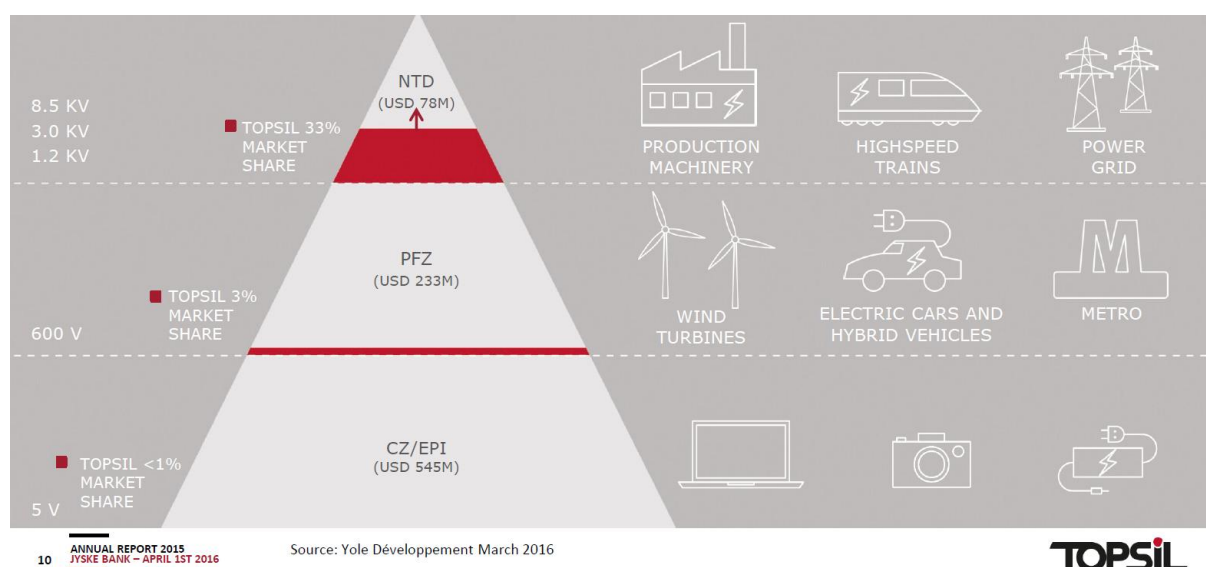


Figure 14: Global Power-Electronics Wafer market⁹⁹

The general trend in the global wafers market is towards increasing wafer diameters. In 2016, the 300 mm and above wafer size-segment held a leading share of the market. Industrial feasibility of NTD for ingots over $\varnothing$ 200 mm and while achieving adequate quality, may raise problems due to the unavoidable neutron-flux gradient in a research reactor. In addition, alternatives to NDT may appear¹⁰⁰. Hence, the future of Si NTD-wafer production in research reactors is uncertain.

5.2.4. Sterilization and food disinfection applications

Single-use medical device sterilization

The majority of the world's sterilization of single-use medical devices and supplies are processed via EO (ethylene oxide) gas, gamma radiation and E-beam radiation. Sterilization of single-use medical devices is conducted on-site within the manufacturer's facility or at an off-site facility operated by a sterilization-services supplier.

The magnitude of the Services market has been evaluated at US\$ 2.4 bn in 2017¹⁰¹. However, this figure encompasses all sterilization methods, including steam and sterilization conducted in hospitals, including reusable-device sterilization. As concerns single-use medical devices¹⁰², the breakdown between the different modalities is roughly 50% for EO, 36%-40% for gamma, and 7% for E-beams. The remaining 5% are miscellaneous modalities such as steam, hydrogen peroxide, gas plasma, nitrogen dioxide (NO₂), peracetic acid (PAA) and some others. In total, there are about 25 known sterilization methods.

⁹⁹ Different wafer substrates: FZ (Floating zone growth process), PFZ (Preferred Float Zone), CZ (Czochralski growth process), EPI (Epitaxy), NTD (neutron transmutation doping)

¹⁰⁰ For instance, gas doped silicon (PFZ) nowadays finds its application in electrical components above 1.2kV, previously requiring NTD silicon, targeting the lower voltage levels. For some power device makers, PFZ seems to be the preferred choice over such NTD, due to the fact that although PFZ substrate performance is well below the tight tolerances of NTD silicon, it does not involve the externally conducted neutron irradiation. NTD SILICON. PRODUCT CHARACTERISTICS, MAIN USES AND GROWTH POTENTIAL. M.G. HANSEN*, C.F. Bjørling (Topsyil)

¹⁰¹ <https://www.marketsandmarkets.com/PressReleases/sterilization-service.asp>

¹⁰² A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Industrial Sterilization of Medical Devices and Healthcare Products. August 31, 2017. GIPA/International Irradiators Association.

The main market players¹⁰³ using ionizing radiation equipment in the Services field are Steris and Sterigenics International¹⁰⁴, which sell Sterilization Contract Services. They use equipment from numerous device manufacturers and source suppliers such as Nordion, for gamma irradiators, and also e-beam and X-ray equipment manufacturers.

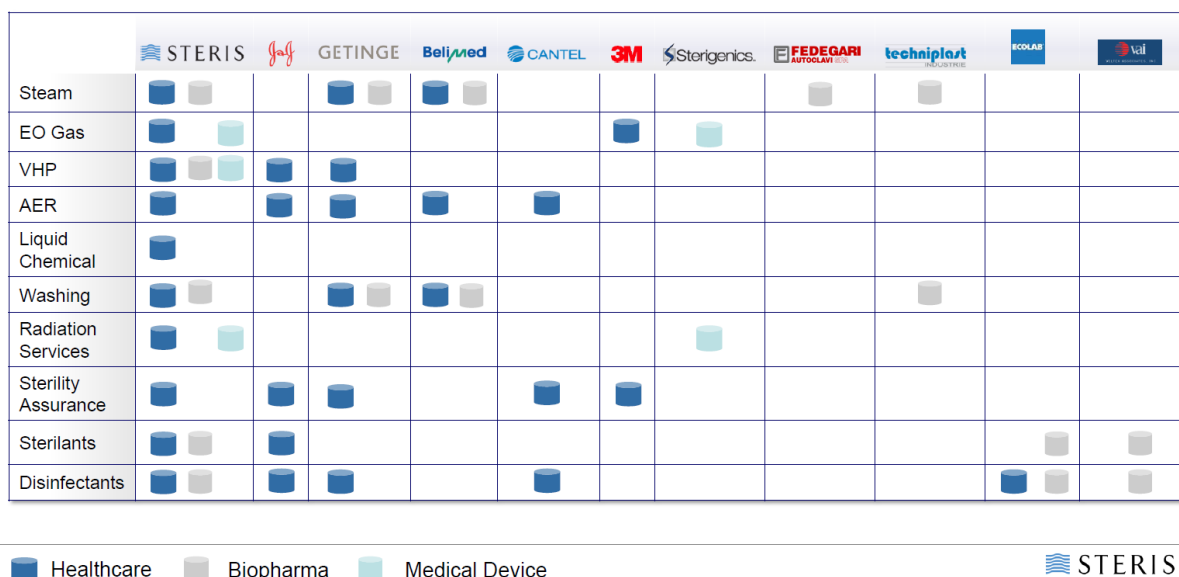


Figure 15: Sterilization and food disinfection market players

Steris announced that their revenues from radiation-technology based Sterilization Contract Services came to about US\$ 440 million in 2017¹⁰⁵. The data for Sterigenics International is not publicly accessible, but its sales are estimated at about US\$ 320 million¹⁰⁶. As these two companies are the market leaders, the global radiation-technology based service market likely amounts to around US\$ 1 bn. As concerns the equipment market, not only does Nordion supply Cobalt-60 (see box below) to companies that sterilize products, they also manufacture irradiation systems. There are over 200 large-scale irradiation facilities in operation in 40 countries. Over 120 have been built by Nordion (sales figures are not publicly available).

In addition, there is an increasing trend among medical-device manufacturers to take sterilization in-house, both for OEM and contract manufacturing. The easiest primary method for in-house use is EO (excluding steam sterilization, which is and has always been primarily in-house), with the next easiest being E-beam. However, *"although it would theoretically be possible for a company to bring in gamma or X-ray processing, it would be uncommon for one to do so due to the larger capital-investment cost."*¹⁰⁷

Food phytosanitary irradiation

Sanitary applications of irradiation, as it is used to reduce the microbial load in spices and herbs or to inactivate pathogens in products of animal origin, had been the most common application in food irradiation until fairly recently. Another application has now emerged as a commercial treatment: the use of irradiation as a quarantine measure to

¹⁰³ Steris Presentation Year 2017.

¹⁰⁴ Owner of Nordion until early 2018. Nordion is being acquired by BWXT.

¹⁰⁵ Steris Presentation Year 2017.

¹⁰⁶ <https://www.owler.com/company/sterigenics>

¹⁰⁷ <https://www.medicaldesignandoutsourcing.com/look-industrial-sterilization-market/>

prevent the spread of insect pests (e.g. fruit flies) which may otherwise take advantage of an increasingly globalized food supply chain to spread to new areas and affect agricultural production. The commercial use of these phytosanitary applications has now reached a significant level. In 2015, 20 000 to 30 000 tonnes of irradiated fresh produce such as fruit and vegetables were marketed in Australia, New Zealand and the United States of America, coming from various countries in the Asia and Pacific region and Mexico.

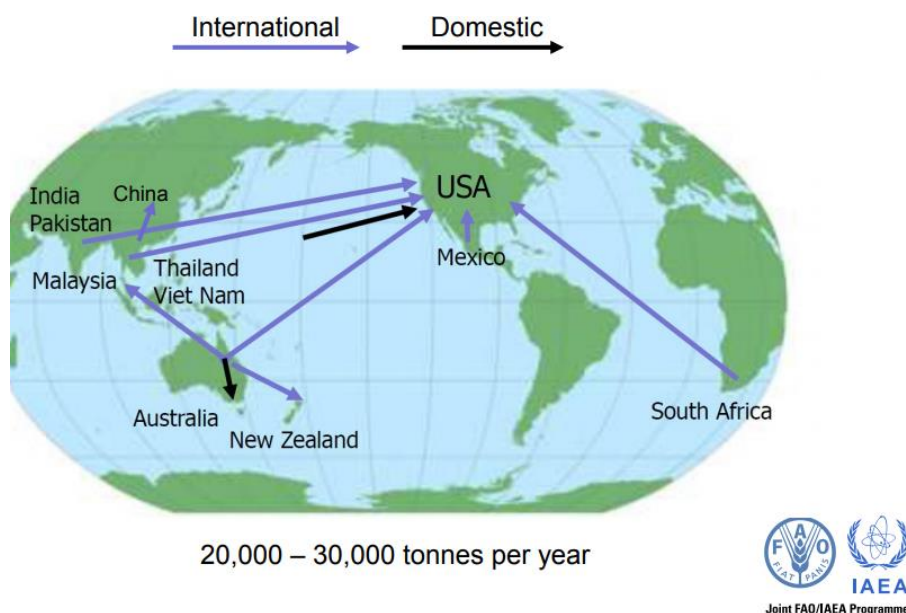


Figure 16 : Fresh fruit and vegetables irradiated at origin or on arrival¹⁰⁸

The quantities of food that are irradiated are growing each year, mainly in the Asia and Pacific region and in the Americas:

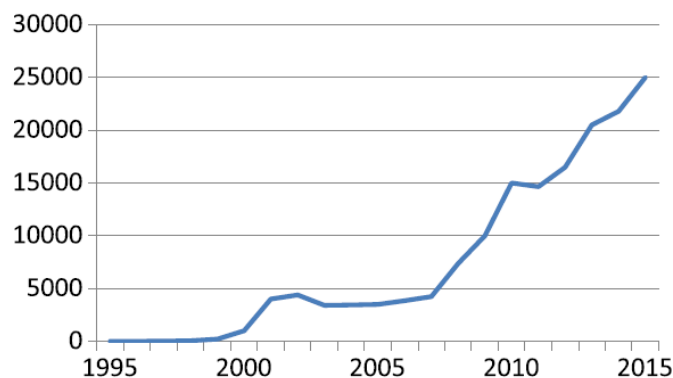


Figure 17 : Tons of produce irradiated per year for phytosanitation worldwide¹⁰⁹

The cost of irradiation depends on the dose (type of source) required, proximity to an irradiation facility and throughput. It can vary widely, from US\$ 30 to US\$ 1970/ton, but can be moderated by efficiencies of scale and high throughputs¹¹⁰. Assuming a maximum of US\$ 2000/ton, the 25 000 tons above would represent a maximum global revenue for

¹⁰⁸ A Global Perspective. Phytosanitary Irradiation. Carl Blackburn 2016. c.blackburn@iaea.org.

¹⁰⁹ Phytosanitary irradiation – Development and application. Guy J.Hallman, Paisan Loaharanu, IAEA/FAO. Radiation Physics and Chemistry 129 (2016) 39–45.

¹¹⁰ <http://canadianfoodbusiness.com/2014/12/17/food-irradiation-adds-cost-makes-sense/>

irradiation services of US\$ 50 m, i.e. far from the sterilization figures for medical devices mentioned above. From the sole market viewpoint, this suggests that food irradiation is not yet a key application. However, as it becomes more economically viable, the number of facilities that specialize in irradiating food increases. Machine sources (electron accelerators and X ray machines) are expected to become predominant over time. Despite the fact that key import markets such as the European Union, Japan, and South Korea do not yet accept irradiation, events indicate that the market may increase significantly over the coming years. China has completed a large electron-beam facility along the southern border in Pinxiang designed for phytosanitary import purposes, which is capable of irradiating 100,000 tons of fruit per year.

Besides food irradiation, there are other agricultural applications: induced mutations in fruit¹¹¹, tsetse sterilization¹¹², the use of radiotracers for soil and water improvements¹¹³, or use in cattle breeding techniques¹¹⁴, most likely of limited commercial value.

Other sterilization applications

Irradiation for sterilization is used in numerous other non-food areas¹¹⁵, such as animal feed, cosmetics, packaging, etc. For instance, a carton food-packages manufacturer¹¹⁶ has installed an e-beam sterilization machine, claiming it provides the same standard of protection as traditional methods but with lower energy requirements and higher throughput. The corresponding equipment-market values are unknown.

5.2.5. Other radioisotope industrial applications (NDT, industrial gauging, etc.)

Applications other than sterilization include NDT Devices, Oil-Well Logging Sources, Wellsite Analysis, Radioactive Material Analysis, Reference & Calibration, Industrial OEM Sources, Medical Sources, and routinely use:

- Selenium-75 (NDT) and Iridium-192 (NDT, Medical);
- Americium 241 (Am-241), for thickness gauging, material analysis, flow gauging;
- Americium/Beryllium (Am/Be) for oil well logging, materials analysis, thickness gauging;
- Californium 252 (Cf-252), for oil well logging, thickness gauging, reactor start-up, fuel-rod scanning, materials analysis, medical applications;
- Caesium 137 (Cs-137) for oil-well logging, thickness gauging, flow measurement, level measurement and medical applications.

Industrial gauging sources containing radioactive sources are used in all industries where levels of gases, liquids, and solids must be checked. IAEA estimates that several hundred thousand such gauges are operating in industry worldwide¹¹⁷.

The industrial gamma-ray radiography industry is highly diverse and consists of a substantial number of individual companies. These range from relatively large companies

¹¹¹ IAEA-TECDOC-1615 Induced Mutation in Tropical Fruit Trees.

¹¹² IAEA-TECDOC-1683.

¹¹³ IAEA-TECDOC-1784 MANAGEMENT AND AREA-WIDE EVALUATION OF WATER CONSERVATION ZONES IN AGRICULTURAL CATCHMENTS FOR BIOMASS PRODUCTION, WATER QUALITY AND FOOD SECURITY.

¹¹⁴ IAEA-TECDOC-1620 Selection and Breeding of Cattle in Asia.

¹¹⁵ A Global Perspective. Phytosanitary Irradiation. Carl Blackburn 2016. c.blackburn@iaea.org

¹¹⁶ Tetra-Laval, with a Comet AG machine.

¹¹⁷ More than 27000 in sole Japan alone. Statistics on the use of radiation in Japan 2012. Japan Radioisotope Association.

offering a wide range of NDT tools and services to small operators specializing in gamma-ray radiography for in-field pipeline inspection, for instance. Moreover, the relatively low cost of gamma sources, their portability¹¹⁸, straightforward image interpretation, and relatively simple radiological-safety measures make entry into the market relatively inexpensive for small companies.

As a result, the IAEA International Catalogue of Sealed Radioactive Sources and Devices (ICSRs) contains 10,000 models, 10,000 device models and 1200 suppliers.

The market volume, including Iridium-192, Selenium-75 and Cobalt-60 sources, is estimated at 19,622 sources in 2015 and should reach 20,813 by 2020¹¹⁹. Since oil and gas represents over 50 percent of the global demand for gamma NDT radioactive sources, the price decline for oil within the past few years has hurt market growth significantly. Among gamma radiation sources, Selenium-75 is expected to provide growth opportunities in the long term due to a softer gamma-ray spectrum than Iridium-192. This trend has been more pronounced in Europe because of more stringent safety regulations. As such, Iridium-192 and Cobalt-60 may be phased out within the next 15 years.

Getting a reliable idea of the market (IR-based equipment and services) was not possible within the framework of this study, due to:

- the variety of uses;
- the mix of medical and industrial applications;
- the nature of the equipment extending from small portable devices to large installations;
- the high portion of services in the market; and
- the number of players, often marketing diverse technologies.

Fragmentary information about to the global radioisotope-sources market are nevertheless given below.

Information about the industrial radioisotopes market

Industrial radioisotopes are used in gamma sterilization irradiators, blood irradiators, non-destructive testing, material modification, gammagraphy devices, as well as gauging equipment.

There are over 100 contract-irradiation service providers in over 30 countries. The main radioisotopes used industrially are Co-60, Ir-192 and Cs-137 among many others. The most common source of gamma rays for irradiation purposes is Cobalt-60, currently produced in CANDU and RBMK power reactors, mainly in Canada, Russia, but also in China and Argentina under long-term supply agreements between the reactor operators and the source manufacturers. India, South Korea, Russia, China, and Japan are largely self-contained markets. For Cobalt-60 and Iridium-192 sealed sources, end users in these countries do not import but rather acquire sources from local manufacturers. The “open” markets are mainly those in the USA and in Europe.

¹¹⁸ The use of portable gamma sources allows radiography to be conducted in remote locations where electric power may not be readily available.

¹¹⁹ <https://ww2.frost.com/news/press-releases/selenium-75-gamma-radioactive-sources-will-sustain-growth-otherwise-struggling-market/>

Due to the lack of sufficient domestic-production means (see appendix A25), the USA imports radioisotopes¹²⁰, coming mainly from Russia and Canada, as well as from two European Research Reactors (BR2, HFR) for Ir-192.

Main Radio-Isotopes imports USA				
Nuclide	Use	Amount/yr	Global demand	Suppliers
Ir-192	Industry	800 000 Ci (enough for about 8000 sources)		Russia, Belgium, Netherlands
Co-60 LSA	Sterilization			Russia, Canada
Co-60 HSA	Radiotherapy			
C-14	Pharmacy	60 to 80 Ci	1500-2500 Ci	Russia
Am-241	Oil & Gas	600 Ci	2000 Ci	Russia

Figure 18: Main radioisotopes imports in the USA

The value of all radioisotope imports into the USA is not publicly available. For Co-60 alone, the annual amount of imports is worth about US\$ 60 m¹²¹, including medical applications.

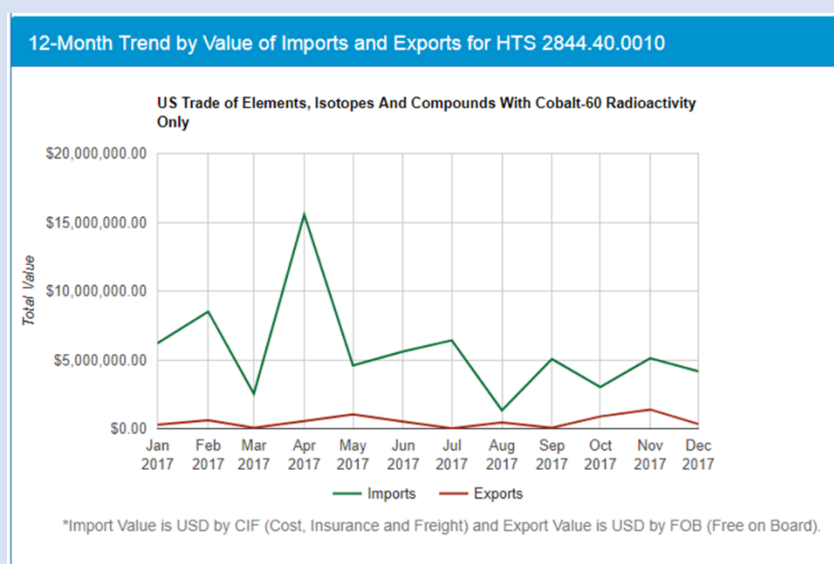


Figure 19: 12-Month trend by value of Imports and exports

Assuming a price of EUR 2400¹²² per 100 Ci Ir-192 source, the cost for 8000 Ir-192 sources would represent about EUR 20 m of imports into the USA. With these assumptions, Co-60 and Ir-192 imports into the USA would together amount to some US\$ 80-90 m. Given that Asian countries are self-reliant, and assuming that the US fill a demand share of at least ½ the market, this would mean that the global yearly “open” market for Co-60 and Ir-192 sources could be valued at US\$ 200 m, at the most.

¹²⁰ U.S. Dependency on Critical Isotopes from Foreign Producers. Mitch Ferren. National Isotope Development Center. Workshop on Isotope Federal Supply and Demand, November 3, 2014.

¹²¹ <http://www.datamyne.com/hts/28/2844400010>

¹²² The BRIT (Board of Radiation & Isotope Technology) of India sells Co-60 (100 Ci) radioactive sources at about Rs (rupee) 373000 (Euros 4600) and Ir-192 (100 Ci) sources at Rs 190400 (Euros 2400) according to their 2014 prices list.

As another yardstick, the global revenues of Rosatom from the isotope business amount to RUB 9823 m (Euros 136 m)¹²³. This figure encompasses both stable isotopes and radioisotopes, as well as medical radioisotopes in addition to industrial ones.

5.2.6. Cargo screening and border-control applications¹²⁴

The detection-systems market may be defined as comprising scanners and related systems, calling on a range of technologies from single or dual X-Rays, CT, Neutron radiography, neutron-induced gamma spectroscopy, nuclear-resonance fluorescence (NRF)¹²⁵ to trace detection as well as nuclear and biological agent detection. Main markets are:

- air transport (cargo, hold baggage, carry-on luggage and passenger screening);
- ports and borders (detection of contraband, drugs, weapons and illegal immigrants);
- defence (detection of explosives, toxic industrial chemicals and other agents);
- and critical infrastructure applications (increasing screening of large numbers of the public, including on mass-transit systems, access to buildings and other screening of personnel).

This market was evaluated at US\$ 3 bn in 2014, up 6-7% per year¹²⁶. A large portion of the market is constituted of services, which include turnkey security screening solutions, with the construction, staffing and long-term operation of security-screening checkpoints, including ports and borders, for instance. This value also includes other technologies, like trace detection as well as nuclear and biological-agent detection, and also encompasses some Defence markets.

Main players in the Security & Detection Civil sector are:

- NucTech (China), and other Chinese suppliers, whose revenues and share of the services market are not publicly available¹²⁷;
- Smiths Detection (UK: 2017 revenues GBP 687 m, Services share: 39%)¹²⁸;
- L-3 Communications—Security and Detection Systems Division (SDS) (USA), civil revenues fraction unknown;
- OSI-Rapiscan (USA), 2017 revenues US\$ 555 m¹²⁹, Services share: about 1/3.
- IBA (Belgium).

Within the market, air transport accounted for nearly half the market in the years immediately post-9/11. Ports and borders are currently becoming the largest segment, accounting for around 35% of the total. The USA and Europe, the most technologically demanding markets, especially for air transport, are now the slowest growing, at around

¹²³ Performance of State Atomic Corporation Rosatom in 2016. Public Annual Report.

¹²⁴ Unless otherwise stated, quantitative items in this paragraph have been obtained from “Smiths Group. Detection systems market”. Edison 2014.

¹²⁵ Using gamma radiation (Prototype).

¹²⁶ Smiths Group. The Risks to Value of Holding on to Detection. Edison, 2014.

¹²⁷ Nuctech claims the position of market leader with a 31.4% market share in 2015. In “Status and Prospect of Application of Radiation Science and Technology in China: a national report”. ICARST 2017. April 2017.

¹²⁸ Smiths Group Annual Report 2017.

¹²⁹ OSI Annual Report 2017

half the market's overall growth rate. It is estimated that the Asian market, by contrast, is growing twice as fast as the average. The distinctiveness of the Chinese market is the widespread use of X-ray scanners on mass transit systems and tourist sites. The acquisition of scale economies from this large and fast-growing domestic market is likely to give to Chinese detection-system companies major advantages at the international level over the coming years¹³⁰.

Only a part of the security & detection market uses ionizing-radiation based tools, especially X-Rays. The X-Ray Security-Screening System Market size was estimated at USD 2 bn in 2016¹³¹. However, due the large portion of Services (namely turnkey solutions, with equipment, construction and operation) in this market, and to unavailable figures for major Asian players, it is not possible to estimate reliably the equipment part of this market.

5.2.7. Other neutron-based industrial uses

In addition to their industrial use in security/detection, industrial gauging or Silicon NTD, neutrons can also be used for imaging and activation analysis.

Neutron activation analysis

Neutron activation analysis (NAA) is used for measuring elements' concentration within a compound. Typically, NAA allows tracing of about 60 elements. NAA is thus widely used for quality control. The total market in Canada and the USA, including the alternative methods, accessible for NAA, was estimated to about US\$ 20 m as of 2010¹³², with over 20 NAA competitors. The unit selling price for the analysis of a sample was quoted at between US\$ 80 /sample for a one-element identification and US\$ 400 for a comprehensive 40 to 60-elements characterization.

Neutron imaging

N-radiography is frequently used at research reactors: it shows impressive results in various fields, such as quality control, ageing of devices analysis and the dynamics of lubrication.

Neutron Computed tomography allows the visualization of the inner structure of the sample. With their ability to penetrate metal casings or other sample environments, neutrons can expose an O-ring placed in sealing joints, for instance, thereby revealing flaws in the inner material caused by their fabrication process. N-radiography enables quality-control services for hydrogenated products such as explosives, or to check explosive actuated bolts for the aerospace industry. Many university research reactors and national laboratories have capabilities for neutron imaging. Like for instance, MURR (Missouri University) and the US/MNRC in the USA, OPAL (Australia), as well as ORPHEE (France) and FRM II (Germany). But they do not generally perform production volume work. Hence, market revenues in these institutions from neutron-imaging remain low, in the low EUR m /year range.

¹³⁰ Smiths Group. The risks to value of holding on to Detection. Edison, 2014

¹³¹ <https://www.gminsights.com/industry-analysis/x-ray-security-screening-system-market-report>

¹³² Development of commercial neutron activation analysis service with a small reactor. C. CHILIAN, G. KENNEDY. École Polytechnique, Montréal, Canada

5.2.8. Consumer products

Radiation technology based consumer products have historically been developed alongside the progress made by the radiation sciences. With the generalised mistrust in these technologies, they tend to be replaced by alternative technologies, although some of them remain more or less widely available.

5.2.8.1. Currently available applications

Widely available applications

Ionisation-chamber smoke detectors (ICSD): the air between electrodes is ionized by a radioactive source. Although some older ionization-chamber smoke detectors that have incorporated Kr-85, Ra-226, Pu-238 or Pu-239 may still be in use, these radionuclides have not been incorporated into ionization-chamber smoke detectors for many years and modern ionization-chamber smoke detectors exclusively use the radionuclide Am-241. An optical smoke-detection mechanism rather than a radioactive source has been developed (detection of smouldering fires). The 1992 publication of the UK National Radiological Protection Board (NRPB) is still in force as the accepted standard for the design, construction and performance of ICSD (with a warning not to dismantle the internal ionization chamber). In France: 7 000 000 ICSD are still in use on more than 300 000 sites (companies and public buildings). ICSD has been forbidden for private households in France since 1966.

Radio-luminous products are used in timepieces, navigational instruments (e.g. compasses), torches, fishing floats and novelty items (e.g. key rings). Weapon sights may also contain gaseous tritium light sources. The use of small, low-activity gaseous tritium light sources in consumer products is expanding. An NRPB standard also exists.

Fluorescent lamp starters: Thorium, Kr-85 and tritium are used by the lamp industry to improve the metallurgical properties of electrodes, to optimize the light spectrum or to provide a starter aid in high-intensity lamps (xenon car lighting and low-wattage specialist lamps). This market is also expanding.

Irradiation of gemstones with E-Beams, gamma or neutrons is a widespread practice.

Less widely available

Electronic devices: voltage regulators, current-surge protectors, spark-gap irradiators and indicator lights contain small quantities of radionuclides, generally to cause ionization and promote current flow.

Thoriated incandescent gas mantles: In the last 20 years, gas-mantle manufacturers have been switching to non-radioactive alternatives from thorium and as a result, the availability of thoriated gas mantles has greatly declined, although some may still be available.

Thoriated tungsten welding electrodes: used in tungsten inert-gas welding techniques. Inhalation of dust particles during grinding is the main concern.

Glassware, tableware, jewellery and ceramic tiles incorporating uranium: may contain uranium compounds incorporated into the glass for the purpose of fluorescence.

Dental products incorporating uranium: Increasingly, non-radioactive alternatives are used and most dental porcelains now no longer contain any radionuclides.

No longer manufactured but may still be in use or available

Static eliminators incorporating Po-210 or Am-241 used for removing dust from photographic negatives, vinyl records, camera lenses and spectacles.

Glass lenses containing uranium and thorium compounds, added at the time of manufacturing to improve certain optical properties. Thorium compounds may also be used in surface coatings to reduce glare or increase reflectivity.

Miscellaneous products such as vending machine coins luminized with C-14 and identity cards luminized with Pm-147.

5.2.9. Market estimate and trends

The sole global smoke-detector market was evaluated to USD 1.31 bn in 2015¹³³; it is rapidly growing, especially in Europe where inhabitants of some MS such as Austria, France, and Germany are massively installing smoke alarms in their homes. However, this figure encompasses diverse technologies (Photoelectric, Ionization, Dual Sensor & Other), and also associated services. Hence, it is difficult to appraise the ICSD share in this market, namely because photoelectric technology is more and more preferred to ionization-smoke detectors for its better performance and also for its easier disposal as compared to ICSD containing radioactive materials.

This smoke-detector example nevertheless shows that the market for ionizing-radiation based consumer products may be far from negligible.

In addition, consumer products may prompt regulations and raise radioactive waste problems.

The EC sponsored a study about these consumer products in 2006/2007. The conclusions which have been drawn from the RP146 study are summarized in the next table, raising questions relative to:

- Testing;
- Standards to be applied;
- Labelling;
- Disposal routes;
- and differences among MS regarding the key issues.

¹³³ <https://www.marketsandmarkets.com/PressReleases/smoke-detector.asp>

Applications	Comments
Currently widely available - Ionisation chamber smoke detectors (ICSD) : air between the electrodes is ionized by a radioactive source (241Am). Optical smoke detection mechanism rather than a radioactive source have been developed (smouldering fires). UK National Radiological Protection Board (NRPB) : That publication is still used as the accepted standard for the design, construction and performance of ICSD. Warning not to dismantle the internal ionization chamber. France : 7 000 000 are still in use on more than 300 000 sites (of companies and public buildings). ICSD for private households forbidden in France since 1966. - Radioluminous products : timepieces, navigational instruments (e.g. compasses), torches, fishing floats and novelty items (e.g. key rings). Weapon sights may also contain gaseous tritium light sources. The use of small, low activity gaseous tritium light sources in consumer products is expanding. NRPB Standard also exists. - Fluorescent lamp starters : Thorium, 85Kr and tritium are all used by the lamp industry to improve the metallurgical properties of electrodes, to optimize the light spectrum or to provide a starter aid in high intensity lamps (xenon car lighting and low wattage specialist lamps). The regulatory body should keep this practice under review - Irradiated gemstones: widespread practice with EB, gamma or neutrons. Prior to the sale of irradiated gemstones to the public, may involve occupational exposure. Import/export procedures ?	RP 146 Conclusions (as of 2007) : • With the exception of the UK, all EU Member States, Candidate States and Accession States report that they have fully implemented the relevant articles of Council Directive 96/29/Euratom. • What is not certain, however, is whether the requirements are effectively enforced. 6.2 Requirements imposed by EU Member States 6.2.1 Product testing • Mandatory product testing is rare and generally it appears that only ICSD are tested to confirm that they conform to standards. • The product standards available (NEA/OECD) are now thirty years old and require updating. 6.2.2 Labelling requirements • Mandatory labelling of consumer products is rare and in most countries where labelling is required this only applies to ICSD. 6.2.3 Disposal requirements • More than half of the countries indicated that controlled disposal (return to the supplier or to the national waste repository) is required for certain products, particularly ICSD. The rest allow disposal of consumer products with the normal household waste. 6.2.4 Prohibitions • There are major differences between the different countries. Some countries do not prohibit any consumer products. Others prohibit, or are planning to prohibit even established products like ICSD. • This approach may cause problems with respect to free trade in Europe, and it is considered that harmonisation of licensing and prohibition is required. 6.3 Type and numbers of products available • It is interesting to note the variation in what is reported as being available in the different countries. • The rise of internet sales means that it is difficult for competent authorities to be aware of every product available in their country. 6.4 Dose assessments made • There were not many dose assessments reported. Only the Netherlands, Spain and the UK appear to have made specific assessments of doses to the public from the use and disposal of consumer products.
Less widely available - Electronic devices : voltage regulators, current surge protectors, spark gap irradiators and indicator lights - Thoriated incandescent gas mantles : In the last 20 years, gas mantle manufacturers have been switching to non-radioactive alternatives to thorium and as a result the availability of thoriated gas mantles has greatly declined, although some may still be available. - Anti-static devices - Thoriated tungsten welding electrodes : used in tungsten inert gas welding techniques. Inhalation of dust particles during grinding is the main concern - Glassware, tableware, jewellery and ceramic tiles incorporating uranium : may contain uranium compounds incorporated into the glass for the purpose of fluorescence - Dental products incorporating uranium : Increasingly, non-radioactive alternatives are used and most dental porcelains now no longer contain any radionuclides	
No longer manufactured but may still be in use or available - Static eliminators incorporating 210Po or 241Am - Thoriated lenses - Miscellaneous products such as vending machine coins luminized with 14C and identity cards luminized with 147Pm	
Lightning preventors Explosives and chemical detectors containing tritium, 63Ni or 133Ba, receiver protection devices (transmit/receive limiters) containing tritium used in radar communications and dust monitors containing 14C, all of which are not normally available for provision to the public	

Table 11 : Consumer products – RP 146A outcomes

It is recommended that the EC updates this last extensive study¹³⁴ on this subject, now outdated, to check which progresses have been made, evaluate better the market and decide on further actions where appropriate.

5.2.10. Industry market: conclusions

Radiation technologies (charged particle beams, X-Rays, gamma-rays, and neutrons) are tools used in many industrial fields like sterilization, manufacturing, NDT and detection or environmental uses. These tools are generally used with other technologies and are embedded into manufacturing processes, products or services by thousands of players worldwide. The manufacturing processes, products and services using these tools generate added value, which exceeds the radiation-based equipment value by several orders of magnitude¹³⁵.

Industry (without Health) US\$ bn	Equipment & Equipment servicing	Services/ products incorporating the equipment
Beam Business	2.2	500
Security/Detection	< 3	
Single use med. devices sterilization	?	1
NDT, industrial gauging	?	?
Radioisotopes	0,2 maximum	?
Silicon NTD	existing reactors	0.08
Food irradiation	?	0.05
Consumer products	to be assessed	
Total	> US\$ 6 bn (EUR 5 bn)	?

Table 12: Ionizing radiation-based equipment market

From the elements gathered in the present overview, the equipment portion of the industrial market (over EUR 5 bn, with a prominent share for accelerators) certainly remains more limited than the Healthcare-equipment market, which was valued at EUR 28.3 bn.

Despite the historically-strong position of Europe regarding the ionizing-radiation field, market leaders in the industrial domains and manufacturers are now predominantly Asian (see China's ambitions, box below) or American companies. This induces a risk of EU-dependence on foreign technology and it is detrimental to Europe's re-industrialization ambitions.

Radiation and Science Technologies in China¹³⁶: Facts and figures

According to the Chinese Nuclear Society, "Radiation Science and Technology (RST) is an emerging strategic industry in China". It has seen rapid development in recent years. More than 400 institutions/companies are engaged in R&D in RST, and several thousand in RST applications by the end of 2016. Annual output exceeds RMB 300 bn

¹³⁴A Review of Consumer Products Containing Radioactive Substances in the European Union. RP 146 A (2007). See Table 1 in particular Products and their reported availability in EU Member States.

¹³⁵"The products that are processed, treated or inspected by particle beams had an annual value >US\$500B in 2010". INDUSTRIAL ACCELERATORS. Robert W. Hamm. IPAC-13. Shanghai.

¹³⁶The elements in this box are taken from a presentation entitled "Status and Prospect of Application of Radiation Science and Technology in China: a national report. Lixin Shen. Deputy Secretary-General Chinese Nuclear Society. ICARST 2017, April 24-28, 2017, Vienna". Even if some asserted figures lack backup details, this presentation shows that China has high ambitions in the Radiation Science and Technology sector.

(US\$ 43.2 bn), or 3 times that of 2010, and maintains an annual growth rate of about 20%. RST has created nearly 100,000 jobs.

Applications are developing at an industry scale in a variety of areas including material-performance improvement by irradiation, radiation processing, radiation-based equipment, public health, public security and environmental protection.

In Radiation science, over 80 research institutions and universities are engaged in RST, supported by a number of facilities:

Type	Name of large-scale facility	Status
Accelerator	HIRFL (Heavy-Ion Research Facility in Lanzhou), 100MeV high Intensity proton cyclotron, 4MeV electrostatic accelerator, dielectric wall proton accelerator used for oncotherapy, proton cyclotron for PET	in operation
	High Intensity Heavy-ion Accelerator Facility (HIAF)	under construction
Reactor	High Flux Engineering Test Reactor (HFETR, 125MW), China Pulse Reactor (CPR, 1MW), Minjiang Test Reactor (MJTR, 5MW), China Experimental Fast Reactor (CEFR, 20MW), China Advanced Research Reactor (CARR, 60 MW), China Mianyang Research Reactor (CMRR, 20MW)	in operation
Light Source	Beijing Electron-Positron Collider (BEPC), Beijing Synchrotron Radiation Facility (BSRF), Hefei Light Source (HLS), Shanghai Synchrotron Radiation Facility (SSRF)	in operation
	Shanghai X-ray Free Electron Laser (SXFEL), China Spallation Neutron Source (CSNS)	under construction
	Beijing Light Source (Gen-IV Light Source)	under planning

Figure 20: Chinese Supporting facilities for research in RST

As concerning radiation technology and equipment:

- R&D in electronic accelerators for irradiation has significantly progressed, and the quantity of radiation equipment grows at an annual rate of over 40 such sets;
- Over 30 radiation-equipment units have been exported overseas, including to the US and to Southeast Asia;
- Cobalt-60 is produced in China, at an annual output of 6 million curies, meeting about 75% of the demand of the Chinese market. By 2015, γ radiation facilities (design capacity >0.3MCi) reached 130 sets, representing 40% of the world's total. The single largest design capacity is 6MCi. The total design capacity is > 170MCi, while actual loading is 70MCi, representing 23% of world's total.

Where industrial applications are concerned, the annual output of the radiation-processing industry reached US\$ 14.4 bn in 2015 with an annual growth rate of 15%, divided among irradiation-induced material modification, radiation processing and radiation equipment. The output of the three sectors amounted in 2015 to US\$ 7.2 bn, US\$ 5.8 bn and US\$ 1.4 bn respectively.

In agriculture, significant progress in radiation-induced mutation breeding of plants is claimed: over 800 mutations in 45 kinds of plants, accounting for 26% of the world's total, have been developed. These radiation-induced mutations have been planted over 20% of China's arable land, with annual crop plantations covering >130 million mu (20 million acres) and contributing 3.5-4 billion kilograms to China's grain production each year. Radiation-processed agricultural products represent half the

world's total, with irradiated products exceeding 400,000 tons in 2015, generating an annual output value of over US\$ 2.6 bn.

Medical equipment and its corresponding uses are developing.

Applications in public security:

- Detection technologies based on X-rays, γ-rays and neutrons see widespread applications;
- Fingerprint-level high precision detection technologies such as Nuclear magnetic resonance, nuclear quadrupole resonance and cosmic muons scattering see bright prospect in applications;
- Large container/vehicle inspection systems have received considerable international acclaim.

In the environmental-applications sector, industrial waste-water treatment using e-Beams has reached the initial stages of industrialization. The newly- developed 5000 m³/d demonstration facility used for deep treatment of waste water from the printing or dying industry has been commissioned for pilot operations and it claims a treatment cost of 35 US cents/m³.

Government support creates a favourable development environment (RST is listed among strategic technologies) and leading enterprises spur rapid development of RST in China (the China Isotope and Radiation Corporation, Nuctech, CGN, United Imaging, Woer¹³⁷, etc.), served by a large domestic market.

5.3. Research

Radiation technologies are key tools for numerous Health and industrial applications. The USA and Asia are dominating the industrial sector.

Radiation-based research hinges around accelerators (X-Ray and charged particle beams), neutrons and radioisotopes.

The first two involve considerable Research infrastructure. The worldwide annualised investment costs of building or revamping major infrastructure over the 2012-2028 period should amount to some US\$ 1.7 bn/year¹³⁸ (EUR 1.5 bn), of which about EUR 0.4 bn for Europe as can be seen from the next table.

¹³⁷ Involved in radiation crosslinked heat-shrinkable material, which has been included in the special major national nuclear technology application plan.

¹³⁸ Construction Projects and Upgrades of Discovery Science Particle Accelerators Worldwide. Based on the latest Accelerator Projects booklet now available from IPAC. Søren Pape Møller, Aarhus University, DK. IPAC-17. Copenhagen, Denmark. May 16, 2017.

Table 13: Short-term Construction and Upgrade costs of major Research Infrastructure (Accelerators & Neutrons)

Project	Country	Laboratory	Constr & upgrades Budget (M\$)	Start	Completed	Const & upgrade Budget annualized
LIGHT SOURCES						
SIRIUS	Brazil		100	2012	2018	14
APS Upgrade	USA	ANL	770	2019	2025	110
LCLS	USA	SLAC	1045	2016	2020	209
AUS SYNCH	Australia	Austral Synchrotron	50	2016	2026	5
SPring-8-II	Japan	SPring-8			5 years	
HEPS-TF	China	IHEP	50	2016	2019	13
ThomX	France	LAL	10	2014	2018	2
FLUTE	Germany	KIT	4		2019	0
ERL	Germany	Uni-Mainz	15	2015	2021	2
XFEL, Flash, ILC, Petra III, PITZ, REGAE	Germany	DESY Center				
ILSF	Iran		300	2015	2025	27
SOLARIS	Poland	Solaris NSRC	50	2011	2016	8
ALBA	Spain	CELLS				
High-Energy Particle Accelerators						
LBNF	USA	Fermilab		2020	2026	0
PIP (proton)	USA	Fermilab	78	2011	2019	9
PIP II	USA	Fermilab	650	2019	2025	93
Super t-Charm	Russia	Budker INP	450		5 years	
HiLUM/HL-LHC	Switzerland	CERN	950	2016	2026	86
LIU	Switzerland	CERN	200	2010	2011	100
Elena	Switzerland	CERN	25	2014	2019	4
FCC	Switzerland	CERN	?	2028	2040	
Nuclear Physics Accelerators						
ARIEL-II	Canada	TRIUMPF	45	2016	2023	6
eRHIC	USA	BNL				0
JLEIC	USA	JLAB	1500	2022	2029	188
FRIB	USA	MSU	730	2014	2021	91
HIAF	China	CAS	500	2017	2024	63
RIBF upg	Japan	RIKEN Nishina Center				0
RAON	Korea	Institute Basic Science	946	2011	2021	86
FAIR	Germany	GSI	1200	2017	2025	133
LNSC Cyclotron	Italy	INFN LNS	11	2017	2020	3
ELI-NP	Romania	IFIN-HH/ELI-NP	67	2014	2019	11
NICA	Russia	JINR	500	2015	2020	83

Project	Country	Laboratory	Constr & upgrades Budget (M\$)	Start	Completed	Const & upgrade Budget annualized
Devices/Test Accelerator						
Cornell-BNL ERL accelerator	USA	BNL	25	2017	2021	5
FACET-II	USA	SLAC	46	2017	2020	12
IOTA/FAST	USA	Fermilab	20	2014	2020	3
bERLinPro	Germany		40	2013	2018	7
MESA	Germany	Mainz	15	2015	2021	2
SINBAD	Germany	DESY	20	2017	2019	7
SPARC_LAB	Italy	INFN-LNF	3	2017	2020	1
ELIMED	Italy	INFN	3	2014	2017	1
AWAKE	Switzerland	CERN	20	2014	2017	5
FCC	Switzerland	CERN		2017	2037	0
CLARA	UK	STFC	50	2015	2020	8
RF Transmitter	Taiwan	NSRRC	0,4	2014	2019	0
ESS Bilbao	Spain	ESS Bilbao	92	2014	2025	8
MEDICAL						
iBNCT	Japan	Tsukuba	25	2011	2017	4
KHIMA	Korea	KIRAMS	195	2010	2020	18
SPES	Italy	INFN-Legnaro	53	2012	2021	5
Accelerator driven systems (transmutation)						
MYRRHA	Belgium	CEN/SCK	320	2018	2024	46
Neutron sources						
HFIR	USA					
ILL	France					
ISIS	UK					
SINQ	Switzerland	PSI				
SNS	USA	ORNL				
JSNS	Japan					
FRM II	Germany					
OPAL	Australia					
China SNS	China	IHEP	251	2011	2018	31
ESS	Sweden	ESS	1840	2014	2025	153
Materials for fusion						
FMIF-AFNS	Japan					0
FMIF-Dones	Europe	CIEMAT	500	2020	2028	56
FUSION						
ITER	International					
Total World (w/o ITER and CERN)			13 764			1 716
of which EU-28 (w/o ITER and CERN)			4 293			453
with CERN			5488			648

5.4. Global economic impact of ionizing-radiation applications

Assessing the global economic impact of such diverse applications is difficult because they are tools generally embedded within products and services, manufacturing processes and research where their specific-added value is virtually impossible to compute. It has nevertheless been estimated that ionizing-radiation applications of accelerators alone underpin nearly half a trillion dollars-worth of commerce a year¹³⁹, without taking into account their invaluable health benefits.

More accessible data is provided by the ionizing-radiation equipment market. Thanks to this yardstick, the global “market” can be evaluated at over EUR 35 bn, of which:

- Health: EUR 28.3 bn;
- Industry (excluding Health): > EUR 5 bn, with the consumer-products segment, which is likely to be significant, still remaining to be quantified;
- Research: EUR 1.5 bn

Healthcare applications are probably the most important non-energy field to use ionizing-radiation tools. The market is growing at 3-6%¹⁴⁰, driven by Asian markets in particular. Competition in these markets is fierce, with an increasing presence of US and Asian companies relying on strong domestic markets.

In Europe, over 1,000,000 workers are monitored by ESOREX for their occupational exposure, of which more than 700,000 in the Healthcare field and 90,000 in the non-nuclear energy industry.

ESOREX 2016	Monitored
MEDICAL FIELD	726 804
INDUSTRY	88 253
NUCLEAR FIELD	129 199
TRANSPORT	1 683
RESEARCH AND EDUCATION	53 474
NATURAL SOURCES	66 897
OTHER FIELDS	2 392
Total	1 068 702

Table 14: Monitored workers in Europe (22 countries)

In addition, Europe’s major medical-technology equipment manufacturers employ over 60,000 people in Europe, a majority of whom work in the IR area, and twice as many as that when considering the jobs induced along the supply chain.

As innovation is the key in this competitive market, substantial investments are needed, triggering synergistic effects with many other technologies, such as IA and big data, for instance, or superconducting materials, thereby creating jobs opportunities for the highly-skilled in Europe.

However, to sustain such assets, investments are necessary. This is the subject of the gap analysis in the following chapters, which is summarized in the conclusion, together with the associated recommendations.

¹³⁹ Robert W. Hamm (R&M Technical Enterprises, Inc.) and Dr.R. Kephart Director, Illinois Accelerator Research Center (IARC), Fermilab. Session TUIA2, IPAC17, Copenhagen Denmark.

¹⁴⁰ CAGR Estimates made by various market analysts often diverge.

6. Health challenges

The Healthcare field is the largest non-energy area to use applications emerging from ionizing-radiation technologies. It concerns over 700,000 monitored professional European users and is part of the everyday lives of all EU-28 citizens. Revolutionary ionizing radiation-based cancer therapy treatments are being developed, promising more personalized, more efficient therapies that increase value for money. Healthcare applications represent the most important opportunities for Europe not only in terms of improved health for European citizens, but also of highly skilled value-added jobs, of sustainable growth and of competitiveness in a market driven by constant innovation and fierce competition.

Medical imaging plays a crucial role in the era of personalised medicine. “You cannot treat what you don’t diagnose”. Imaging and therapy are essential complementary Healthcare applications arising from ionizing-radiation technologies. Ionizing-radiation imaging is used for a number of clinical indications, while oncology is the privileged domain of ionizing radiation-based therapies. Many types of radiation are used, including low-energy X-Rays or γ -Rays for imaging, higher doses of X-Rays, γ -Rays or ions for external beam radiotherapy, photon and β emitting sources for brachytherapy, and α or β particles for targeted therapy at the molecular level. Accelerators produce X-Rays and ion beams, while γ -Rays, α and β particles are due to decay of radioisotopes, generally created in radioisotopes-production research reactors or in cyclotrons.

All these techniques are complementary, either from the perspective of clinical indications, efficacy or cost-savings. For instance, PET/SPECT allows functional imaging of the body whereas radiography shows morphological features. These applications are increasingly combined for the greater benefit of human health.

Radiation type	Radiation source	Imaging	Therapy	Combined imaging/therapy
X-Rays	Accelerator	External Beam X-Rays (CT, ...)	External Beam or Brachytherapy X-Rays	
protons, ions, electrons	Accelerator		External Beam or Brachytherapy	
γ - Rays	Radioisotopes	SPECT (Mo-99/Tc-99m,...)	External Beam or brachytherapy γ -Rays	Nuclear medicine Theranostics (Imaging for screening the patient, NM therapy with same molecule, then re-imaging for efficiency check and react)
		Cyclotron produced β^+ γ emitters PET (F-18,...)		
α , β emitters			Therapeutic radiopharmaceuticals labelled with (α , β , γ emitters)	
Combinations of different technologies & radiations		PET/CT, SPECT/CT, MRI/PET	IORT (Surgery + Radiotherapy)	MRI (Magnetic Resonance Imaging) + Linac

Figure 21: Examples of the multiple uses of radiation in Health

Use of these technologies also presents a series of challenges:

- health risks resulting from exposure, particularly in CT. Even if significant progress has been made (modern legal framework, advances in technology, etc.), challenges remain associated with the ever-expanding use of imaging, rapid innovation, etc.;

- increasingly complex technologies are raising questions about the investments required to renew equipment and to adapt skills.

In view of its potential impact on Health, Healthcare system finances and the European economy, an emerging technology such as Nuclear-medicine therapy deserves to be supported.

6.1. Quality and safety of EU-28 radiology

*More details on Computed Tomography can be found in Appendix A.2
on Interventional Radiology in Appendix A.3
on human-resources challenges in Appendix A.4.*

Since their discovery in 1895, the use of X-rays for imaging has become the most common method of medical imaging. On average, every European citizen benefits from an X-Ray imaging procedure every year.

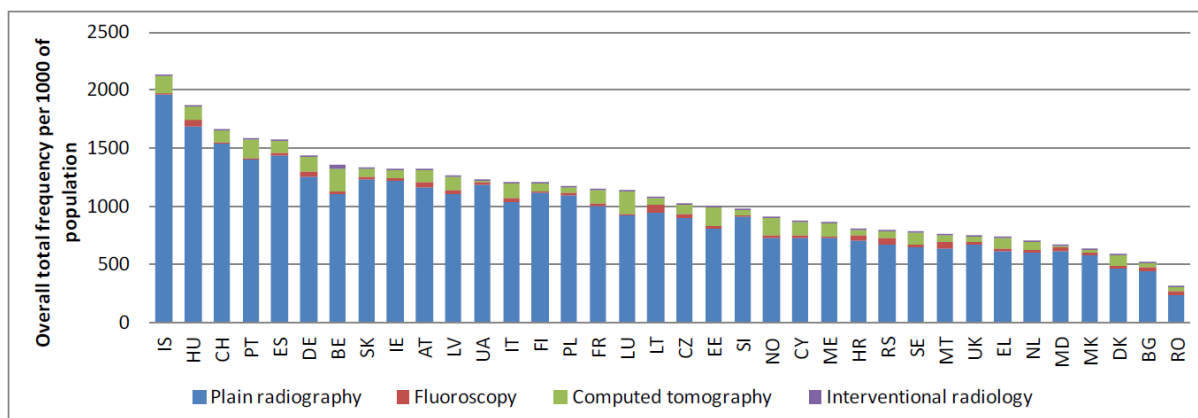


Figure 22: Frequency of use of diverse X-Rays modalities across Europe. Source: RP 180

There are many X-Ray imaging techniques. Dental radiography is commonly used in the diagnoses of oral-cavity problems. Projection radiography produces two-dimensional images of the skeletal system and of soft tissues. The very common chest X-Ray can be used to identify lung diseases, the abdominal x-ray can detect obstructions, free air and free fluids. X-rays may also be used to detect pathologies such as gallstones or kidney stones or to evaluate how an orthopaedic implant such as a knee, hip or shoulder replacement is situated in the body. The use of contrast agents enables generating images of the cardiovascular system. In computed tomography (CT) scanning, images or slices of specific areas of the body are obtained from a large series of two-dimensional X-ray images taken in different directions, which are combined into a three-dimensional image of the inside of the body using complex IT for use in diagnostics and for therapeutic purposes in various medical disciplines. Fluoroscopy is an imaging technique commonly called on by physicians or radiation therapists to obtain real-time moving images of the internal structures of a patient. X-Ray imaging is also widely used in Interventional Radiology and Cardiology. In Interventional Radiology, it provides a minimally-invasive imaging tool to target and display the results of a surgical intervention. While Interventional cardiology, for its part, relies on catheter-based techniques making use of real-time X-Ray imaging (fluoroscopy...).

However, in contrast to these invaluable health benefits, X-Ray imaging, and CT in particular, is responsible of more than 80%¹⁴¹ of human-induced ionizing radiation doses received by the population. In application of the dose-justification principle, Authorities, equipment manufacturers, professional organisations, and medical professionals have already taken actions to enhance radioprotection, develop improved equipment and prevent unnecessary exposures (unjustified and sub-optimal use of X-Ray imaging).

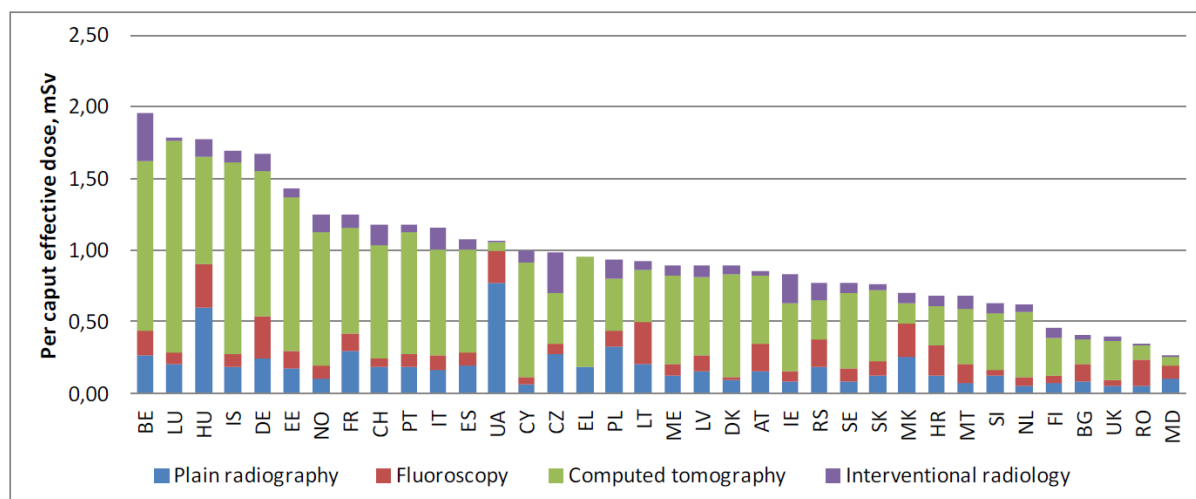


Figure 23: Effective doses in Europe per capita. Source: RP 180

6.1.1. EC initiatives

In the Research field, the H2020 programme addresses the question of low doses: the EIBIR (European Institute for Biomedical Imaging Research) Medirad project on Implications of low-dose medical radiation exposure or the CONCERT programme (MELODI, EURADOS, ALLIANCE, NERIS).

With its continual concern for the safe use of radiation technologies, the EC issued a series of landmark regulations which were recently updated by the Basic Safety Standards (BSS) Directive 2013-59 Euratom. The BSS Directive introduces several changes with respect to the radiation protection of patients, including requirements for dose recording and reporting, provision of information to patients and users of medical equipment, and prevention and learning from accidental exposures. Member States were to bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 6 February 2018.

6.1.2. Manufacturers and Safety Authorities initiatives

Regular discussions have been held as of 2010 between COCIR¹⁴² and the Heads of European Radiation Competent Authorities (HERCA) requesting the industry to commit to reducing radiation doses from CT equipment. A dedicated COCIR Task Force was created to respond to HERCA's request and a COCIR CT manufacturers' voluntary commitment was released in May 2011. As a result, COCIR CT manufacturers have been developing

¹⁴¹ Diverse figures can be found in the literature, all above 80%

¹⁴² European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry.

and providing dose-reduction features on CT systems for many years. This trend continues today¹⁴³.

However, technological improvement must also be implemented at the practical level by users. This raises the question of the renewal of equipment in radiology centres. According to COCIR, excessive ageing of equipment in EU-28 Member States does not allow them to capture the immediate benefits of the technological improvements available.

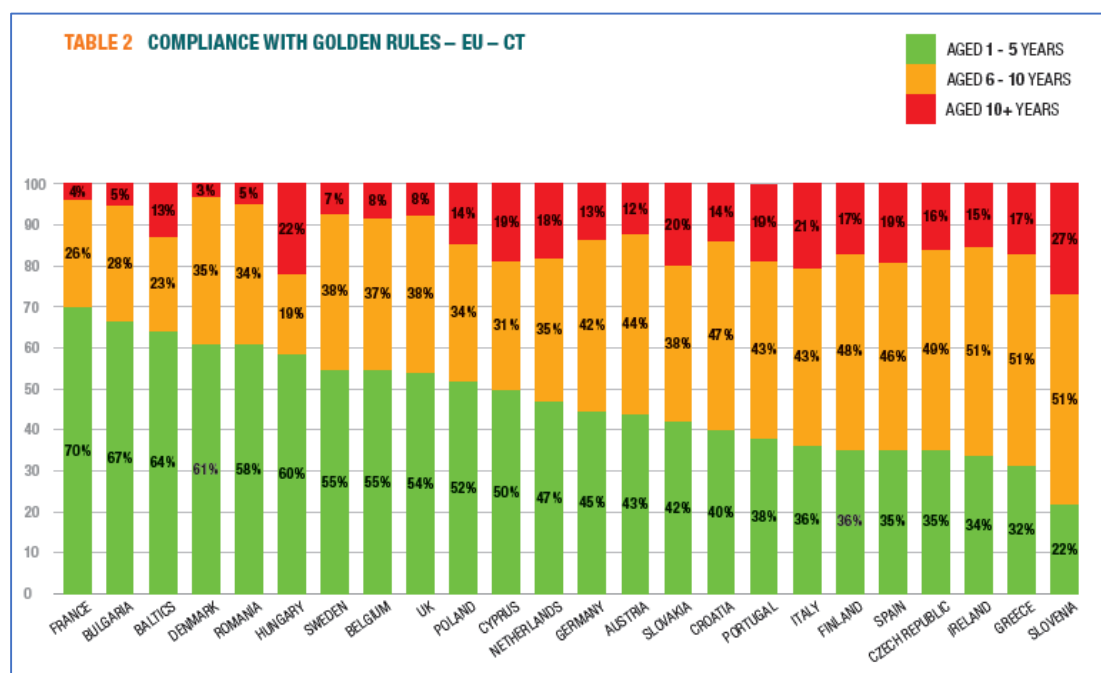


Figure 24: Age range of CT equipment in Europe – Source COCIR

Moreover, dose-saving features are not necessarily equipping new equipment, being marketed as “extra” features. The major risk is the development of a two-tier system. The USA recently developed the NEMA X-29 standard for CT equipment along with the CT Dose Differential Payment Policy, which establish a dose-optimization standard and offers an incentive for providers to meet that standard. It is recommended that a comparison between this approach and the European one be conducted, taking into account the limited financial impact of renewing the equipment (see box below). As technology evolves rapidly, there is a need for continuous and equipment-specific training of users, to fully integrate innovations into daily use of equipment. The main equipment manufacturers offer training courses.

Portion of Ionizing Radiation-based Imaging Equipment in European Healthcare expenses

According to MedTech Europe¹⁴⁴, the European MedTech market per capita represented about EUR 195 yearly in 2013 as compared to EUR 2645 in European Health expenses per capita¹⁴⁵ and can be compared to other expenses.

¹⁴³ with Patient Protocol Selection Guidance, Automatic Tube Current Modulation (ATCM) and X-ray Initiation, Precise X-ray Field shaping, Dose Efficient Design, Dose reporting and Awareness, Training Opportunities, Paediatric Protocols, Dedicated Infant Imaging Mode, Advanced Tube and Collimator Design, Dose Efficient Detection, Dose Display and Recording and Optimized Image Reconstruction.

¹⁴⁴ MedTech Europe: European Medical Technology in figures.

¹⁴⁵ Figures given for the last year available (not indicated), with Switzerland and Norway added

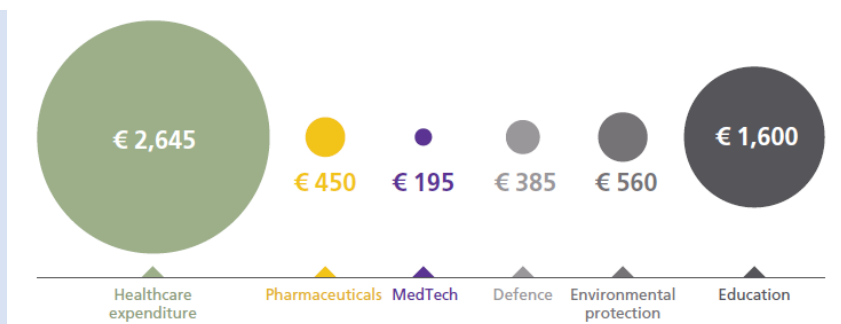


Figure 25 : Relative importance of MedTech equipment as compared to other significant figures

More recent global European health expenses can be retrieved from Eurostat (http://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_expenditure_statistics) and came to EUR 1459 bn in 2015, corresponding to 9.9% of EUR 14728 bn in GDP at current market prices.

Annual expenses for European ionizing radiation-based imaging equipment (all modalities, excluding equipment servicing) amount to EUR 3.5 bn, i.e. 2.4‰ of health expenditures, or EUR 7 compared to EUR 2879 in health expenditures per European inhabitant.

6.1.3. Avoid unnecessary CT exams

On the medical side, many efforts remain to be made to achieve adequate awareness levels, appropriateness and audit practices. Beyond equipment renewal, different studies in the last few years (in Finland, Sweden, Luxembourg and in the USA) showed that a considerable number of CT exams conducted were not needed or could be replaced by other imaging techniques such as MRI or ultrasounds. Such excessive CT prescribing can be due to various reasons, including lack of communication between medical centres hence forcing duplication of exams or because of patient expectations as CT exams have become standard in public opinion.

Sweden conducted a national survey¹⁴⁶ in 2006 about justification for CT examinations, indicating that approximately 20% of all examinations should not have been carried out or should have been done using another imaging modality such as MRI or ultrasound. In a follow-up study in 2011¹⁴⁷, Sweden focused on paediatric CT examinations. This study showed a considerable level of disagreement about when to perform a CT examination in paediatrics, since reviewing physicians only agreed with the radiology department's choice of examination in 51% of the cases.

Luxembourg, having recognized the high frequency of radiological procedures, which resulted in a high total collective effective dose, conducted a national audit¹⁴⁸ in 2016 to evaluate the quality of the referrals and their compliance with its national legislation. The results of the audit indicated that the compliance rate of referrals for medical imaging in Luxembourg is unsatisfactory overall (19 % of the referrals did not

¹⁴⁶ Swedish Radiation Safety Authority: National Survey on Justification of CT examinations

<https://www.stralsakerhetsmyndigheten.se/en/publications/reports/radiation-protection/2009/200903/>

¹⁴⁷ Swedish Radiation Safety Authority: Radiological examinations of children: a study of method options;

<https://www.stralsakerhetsmyndigheten.se/publikationer/rapporter/stralskydd/2016/201614/>

¹⁴⁸ National audit on the adequate completion of medical imaging request forms in Luxembourg;
<https://www.iaea.org/sites/default/files/18/02/rpop-session1.pdf> , pp. 13-16.

include information about “clinical background” and “question to be asked”) and that the quality of the referrals must be improved, largely through further education and training of the referrers.

Another national audit¹⁴⁹ was conducted by Luxembourg in 2017 in order to evaluate the appropriateness of CT and MRI examinations based on their national referral guidelines. The results indicated that the appropriateness was higher for MRI than for CT referrals (79% vs 61%). It was also evident that for CT, the appropriateness rates were better in the case of paediatric than for adult referrals and when referrals were requested by medical specialists rather than by general practitioners.

Following the 2012 Bonn Call for Action published by the International Atomic Energy Agency (IAEA) and co-sponsored by the World Health Organization (WHO), ESR150 emphasised in 2014 quality and safety, education and training, research and e-Health. The ESR Call to EU institutions to support its 2014 “European Action Plan for Medical Imaging to improve quality of care and patient safety” is given in appendix 20.

This plan was recently complemented by an updated ESR EuroImaging Call for Action¹⁵¹. The mission of EuroSafe Imaging is to support and strengthen medical-radiation protection across Europe, by bringing together European medical-imaging entities (the European Society of Radiology, European Federation of Radiographer Societies, European Federation of Organisations for Medical Physics, Cardiovascular and Interventional Radiological Society of Europe, European Society of Paediatric Radiology, etc.) and National radiology societies.

This plan has the following objectives.

1. Development of guideline implementation policies and dissemination of a Clinical Decision Support system (ESR iGuide) in Europe
2. Development of clinical diagnostic reference levels (DRLs) for adults and children
3. Development of image-quality assessment based on clinical indications
4. Promotion of dose-management systems to establish local DRLs and beyond
5. Development of performance indicators for radiation protection management
6. Implementation of a clinical audit tool for using imaging to improve the quality of patient care
7. Radiation protection of children: development of guidance for the appropriate and safe use of imaging, as well as of good communications
8. Dialogue with industry regarding improvement of radiological equipment, the use of cutting-edge equipment (e.g. Dose Management Systems) and the harmonisation of exposure indicators
9. Strengthening the EuroSafe Imaging Stars network of imaging centres that embody best practice in radiation protection
10. Organisation of radiation-protection training courses and development of e-learning material to promote a safety culture and raise awareness about radiation protection
11. Facilitation of research into advanced radiation-protection topics, e.g. artificial intelligence, dissemination and translation into clinical practice
12. Improvement of information for and communication with patients as regards radiological procedures, related benefits and possible risks
13. Commitment alongside stakeholders and collaboration with related initiatives and regulatory authorities in Europe and beyond to contribute to a worldwide safety culture in the medical-imaging field

Table 15: Eurosafe imaging plan (ESR)

¹⁴⁹ National audit on the appropriateness of CT and MRI examinations in Luxembourg;
<http://www.sante.public.lu/fr/publications/a/audit-conformite-examens-imageriemedicale-volet-b/index.html>

¹⁵⁰ European Society of Radiology

¹⁵¹ Press release from Pr. Frija, former ESR President, EuroSafe Imaging Steering Committee Chair. See also ESR Site <https://www.myesr.org/> and <http://www.eurosafeimaging.org/> for more details

6.1.4. Human-resource challenge in Radiology

More details on human-resource challenges can be found in Appendix A.4.

Europe is currently experiencing a complex demographic transformation that is applying increasing pressure on healthcare resources across the continent. Specifically, there is a widening capacity gap in the field of radiology driven by a steady increase in the demand for cross-sectional imaging (CT and MRI) and a stagnant number of trained radiologists available to provide analysis reports on these images. This is causing a significantly heavier workload for consultant radiologists and points up an unparalleled capacity challenge in radiology. European governments and institutions need to address this issue as a matter of urgency. The challenge is significant and is manifested differently across European countries.

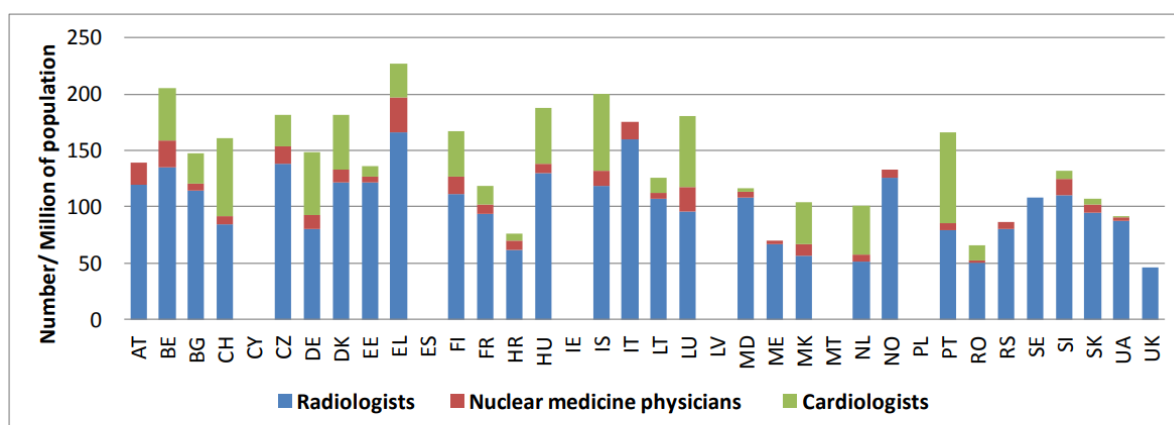
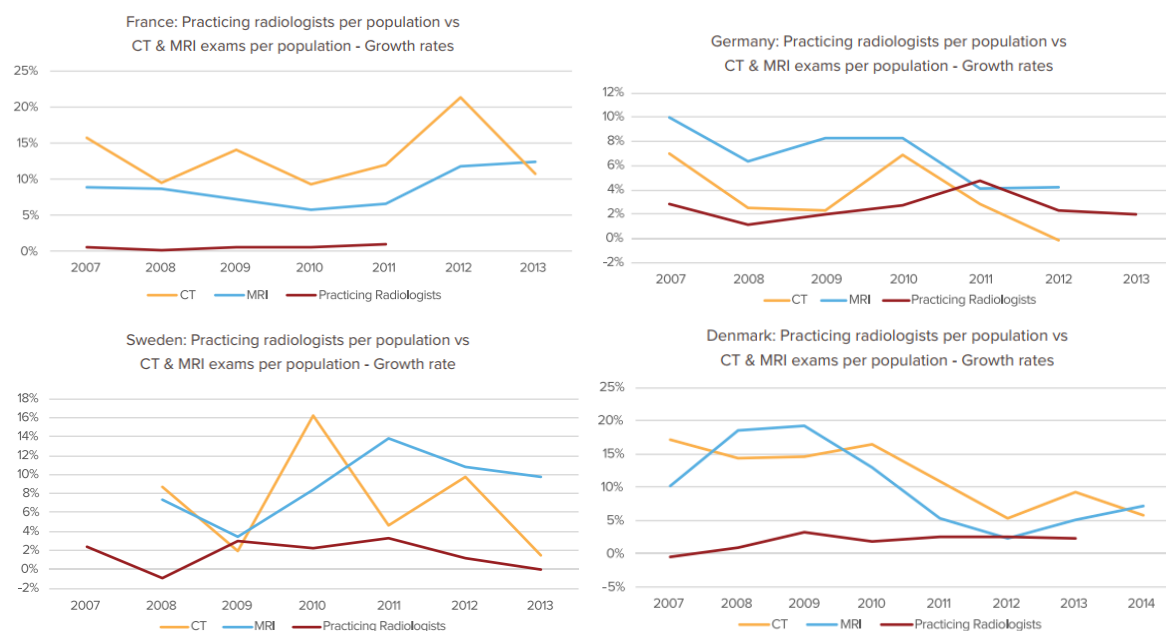


Figure 4.2. Numbers of specific health care professionals, per million of population. In case of no number, no information from the country has been available



Source: RP180 (up) & Europe's looming radiology capacity challenge – a comparative study, C. Silvestrin, United Kingdom, France, Germany, Sweden & Denmark - TMC (down)

Figure 26 : Radiologists status among EU-28 Member States

Among other methods, teleradiology could potentially provide a technical solution to this shortage, enabling radiologists in the EU to work more efficiently. Despite a wide variety

of existing teleradiology applications in Europe, implementation mainly occurs in countries with a high concentration of networked PACS (Picture archiving and communication system), thus limiting its practical dissemination.

Language remains an unresolved issue and a limiting factor for further deployment of such services.

As concerns cross-border services, there is a great demand for focused pan-European legislation, appropriately-adapted price regulation and a quality-assurance framework.

In short, the ESR would support future EU legislation covering the following:

1. Defining teleradiology as a medical act in its own right.
2. Establishing EU-wide accreditation criteria for teleradiology providers.
3. Emphasising the importance of delivering high-quality health care.
4. Applying international quality standards, including oversight of service providers.
5. Regulating teleradiology as being the responsibility of the member state in which the patient undergoes the imaging procedure.
6. Providing full information to patients and obtaining their informed consent for the use of teleradiology.

It is recommended that the EC examines the opportunity of developing such legislation.

6.2. Quality and safety of EU-28 radiotherapy

*More details on external radiation therapy can be found in Appendix A.5,
for Brachytherapy in Appendix A.6*

Cancer treatment uses a combination of different approaches: surgery, radiotherapy, therapies using high-energy radiation to shrink tumours and kill cancer cells, systemic treatments (including chemotherapy & hormonal treatment), and immunotherapy (currently under major development).

As is the case in radiology, radiotherapy technologies are constantly progressing and becoming increasingly complex, integrating more imaging devices and ever-greater IT. As about half of all cancer patients should be receiving some kind of radiotherapy as part of their treatment, challenges arise among the MS regarding equipment dosage rates, the ageing of installed equipment, and the training and education of staff needed to conduct these complex treatments.

6.2.1. Radiotherapy is becoming increasingly complex...

X-ray external radiotherapy is the most common method of radiotherapy for cancer treatment. Taking the UK as an example, with its population of around 64 million people, approximately 130,000 patients are treated each year using some 300 linear accelerators; more than half of these treatments are for breast and prostate cancer. Each X-ray-treatment machine delivers around 7,000 therapy sessions a year.

Echoing the progress made in X-Ray imaging technologies, radiotherapy equipment suppliers continuously improve the performance of their products, with three main objectives:

1. Ever more **accurate delivery of X-rays to tumours**: X-rays can penetrate to reach deep-seated tumours, and one of the main challenges of radiotherapy using X-rays is to minimise the collateral damage to healthy surrounding tissues, particularly vital organs. The result is that the majority of radiotherapeutic procedures now employ state-of-the-art, computer-controlled treatment methods that enable a precise radiation dose-volume to be delivered while sparing surrounding tissues and organs at risk. These techniques — intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) — allow the radiation to impinge on the target area from several directions, or fields, and create a radiation volume that encapsulates the target. Much of the sophistication of these machines lies in the close connection between the treatment plan — obtained from suitable imaging and planning software — and subsequent beam-control to deliver that plan accurately and safely. This will be possible by detecting the transit dose behind the patient. Transmitted radiation is attenuated in the patient and can be acquired with flat panel detectors and used for online dose verification and patient positioning.
2. **Combined imaging and therapy**: The availability of increasingly accurate, high resolution images, tissue contrast and functional analysis, obtained with imaging techniques such as axial computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) provide the following advantages:
 - the ability to achieve a better definition – in 3D – of the volumes to be treated and organs to be protected;

- the ability to take into account external and internal anatomical movements in 4D – that is, over time as well as in 3D space (e.g. with the MRI-linac);
 - the ability to distinguish volumes of functional biological significance, by combining images made by complementary techniques, depending on what is required, particularly for focal treatment (e.g. in prostate cancer).
3. **Personalised planning:** Further improvements include items available to reduce the risk that a treatment differs from the prescription, for example:
- “solid” treatment planning and delivery, taking into account uncertainties;
 - the use of images in the treatment room – image-guided radiation therapy (IGRT);
 - the control of doses administered to patients (dosimetry “in vivo” and/or “transit”);
 - adapting treatments to changes such as patient morphology (“adaptive radiotherapy”).

Other ongoing technological developments also include:

- The integration of measuring devices for dose reconstruction (for example, transit dosimetry, prompt gamma, acoustic signals);
- Research on radiation biology, including biometry;
- The implementation of new delivery systems (for example, micro-strips, ‘flash’ or very high dose-rate irradiation);
- The use of radio-sensitizers and radio-protectors (for example, nanoparticles, which can accumulate in tumour tissues);
- The use of “big data” as “smart data” (e.g., for diagnosis, treatment strategy, automatic planning and optimised quality assurance);
- The reduction of accelerator costs;
- The increase of reliability/availability for operating in challenging environments. It has been estimated that the annual global cancer incidence rate will rise from 15 million cases in 2015 to as many as 25 million cases in 2035, 65 to 70 per cent of which will occur in low- and middle-income countries (LMICs) where there is a severe shortfall in radiation-treatment capacity. Modern, effective radiation therapy in LMICs requires radiation-therapy machines that can deliver sophisticated treatment in an environment with a challenging infrastructure and/or a shortage of personnel.

The continuous innovation trend, necessary for both improved efficiency of the treatments and competitiveness on export markets, presents challenges at the human resource level, in work organization and as to equipment renewal.

6.2.2. Radiotherapy: human resources, work organization and equipment challenges

The demand for radiotherapy facilities is steadily increasing, with most new machines having an IMRT or a similar delivery method, and with many incorporating image-guidance.

In Europe and more widely, capacity needs have been forecast in several studies that include the EU-funded project QUARTS (Quantification of Radiation Therapy Infrastructure and Staffing Needs) and the ESTRO-HERO (Health Economics in Radiation Oncology) project.

The results of the HERO survey document a significant contrast in the access to modern radiotherapy equipment in Europe. Although the European average number of MV machines per million inhabitants and per department is now better, in line with QUARTS recommendations from 2005, there is still a significant contrast in the access to radiotherapy equipment in Europe. While high-income countries, especially in North-western Europe are well-served with radiotherapy resources, other countries are facing important shortages of both equipment in general and especially machines capable of delivering high-precision conformal treatments (IMRT, IGRT).

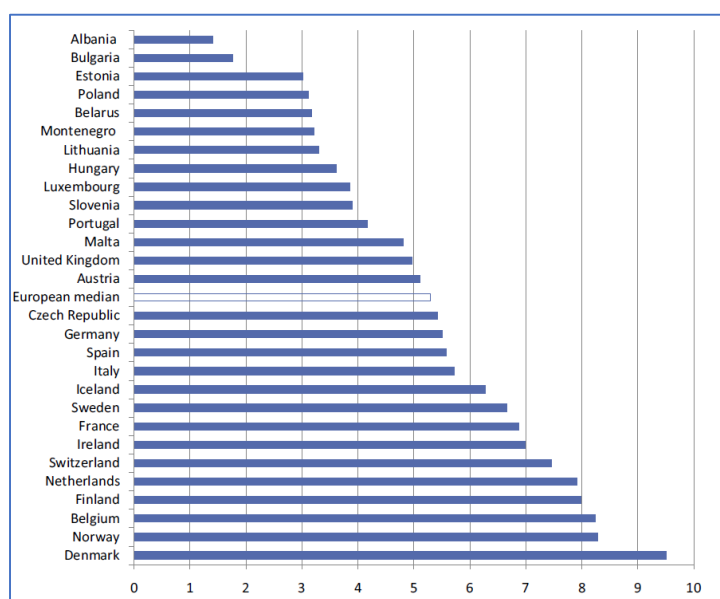


Figure 27: Average number of radiotherapy treatment machines (MV units) per million inhabitants in 28 European countries (ESTRO Survey¹⁵²)

Radiotherapy also requires highly skilled personnel: Radiation Oncologists (RO), Medical Physicists (MP) Dosimetrists (DO), radiation therapists (RTT), radiotherapy nurses (RN). HERO enables documenting these professionals practicing across Europe, including examining their workload and work organization (see below).

¹⁵²Radiotherapy equipment and departments in European countries: Final results from the ESTRO-HERO survey. Radiotherapy and Oncology 112 (2014) 155-164

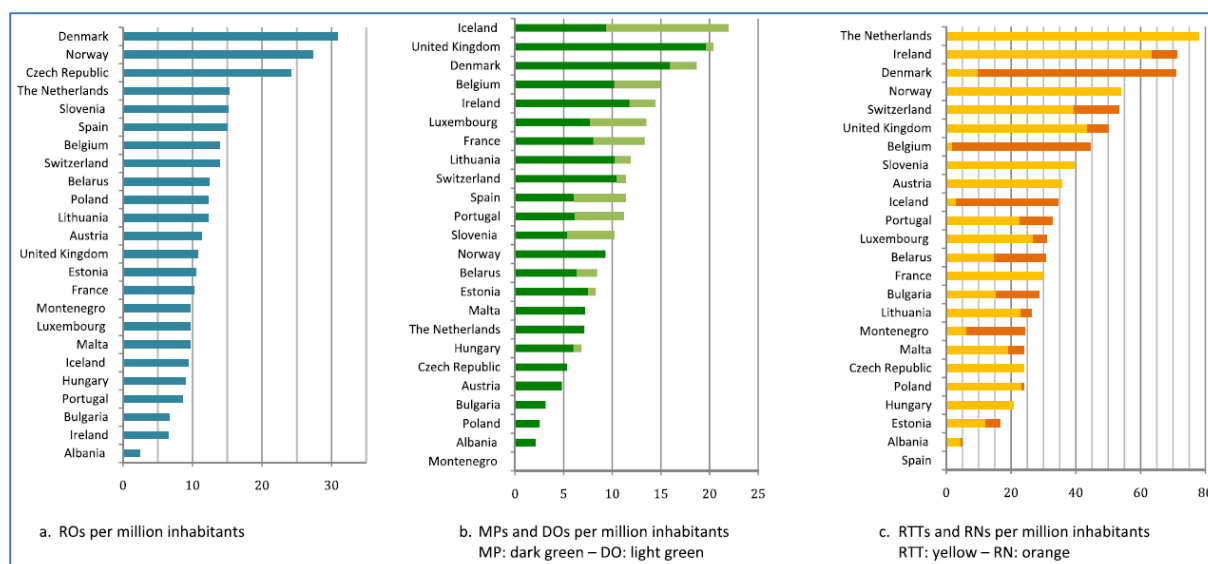


Figure 28: Numbers of different personnel categories per million inhabitants¹⁵³

There are contrasting situations among the MS in terms of workload/work organization: Radiation oncologists on average deliver 208.9 courses of treatment per year (range: 99.9–348.8), physicists and dosimetrists jointly deliver 303.3 courses (range: 85–757.7) and RTT and nurses 76.8 (range: 25.7–156.8). In countries with a higher GNI (Gross national income) per capita, all personnel categories deliver fewer courses of treatment per year than in less affluent countries. This relationship is most evident for RTTs and nurses.

The HERO surveys make it possible to conclude that average personnel figures in Europe are now consistent with the 2005 QUARTS recommendations, or even more favourable, but a considerable variation in available personnel and courses delivered per year persists at the highest and lowest staffing levels. This not only reflects the variation in cancer incidence and socio-economic determinants, but also the stage in technology adoption, along with treatment complexity and the different professional roles and responsibilities within each country. The HERO data underpin the need for accurate prediction models and long-term education and training programmes.

According to ESTRO, the efficient provision of safe, high-quality radiotherapy services would benefit from the availability of well-structured guidelines for capital and human resources, based on agreed metrics, which could be linked to detailed estimates of requirements.

At the same time, to face the increasing complexity of radiotherapy equipment and treatments and in order to deal with the risk of using them as “black boxes”, ESTRO identified needs for improved training and education, and took a number of initiatives¹⁵⁴.

¹⁵³ ESTRO HERO Survey Radiotherapy and Oncology 112 (2014) 178-186

¹⁵⁴ Competencies in radiation oncology: A new approach for education and training of professionals for Radiotherapy and Oncology in Europe. Radiation and Oncology (2012) 1-4

As concerning human resources and work organization questions in radiotherapy centres, it is recommended that

- an evaluation be conducted to determine to what extent the BSS Directive (which had to be transposed by early 2018) is now applied
- the EC supports the development of guidelines relative to human resources and radiotherapy departments organization. Such support might be in the form of a collaboration with national authorities and other bodies, a communication to Health Authorities, an assessment of the impact of EU policies on these subjects or regular statistics and reporting on the size of inequalities in the EU and on successful strategies to reduce them.

HERO's actions continue, ranging from the development of economic models to computing the value for money of RO treatments, which will enable users to:

- Evaluate and compare the cost-effectiveness and cost-utility of different RO treatments and techniques (new versus standard techniques, RO treatments vs. other oncology treatments);
- Perform different estimates on gains in outcome, different costs, different countries, different radiotherapy techniques;
- Compare RO cost-effectiveness with those obtained for other oncology treatments in order to position radiotherapy within the general oncology landscape.

ESTRO is engaged in the assessments of the national costs of radiotherapy delivery¹⁵⁵. This initiative could be actively supported by the EC.

6.3. Protontherapy challenges

More details on Protontherapy can be found in Appendix A.7, along with Carbon-Ion therapy in Appendix A.8 and Other Therapeutic applications in Appendix A.9

Besides X-ray therapies, two rising technologies are emerging: protontherapy and nuclear medicine, presenting specific challenges.

Therapies using accelerated-particle beams have growing potential in dealing with difficult-to-treat tumours, for example because of the risk of damaging neighbouring sensitive tissues such as the spine or other organs. Also, some treatments may benefit from the use of particles that deliver doses having a greater radiobiological efficacy (RBE), notably carbon ions.

Proton-therapy centres are now widely distributed across Europe, and high-energy facilities suitable for children and adults' treatments are listed below. Germany and Italy not only have the majority of proton centres but also offer the only ion-beam treatments currently available in Europe. Many new centres are currently under construction in Europe, as in the rest of the world, namely the USA and Japan.

¹⁵⁵ RADIOTHERAPY CURES CANCER TODAY. Help us close the gap in access to treatment. 5 December 2017. European Parliament, Brussels

Czech Republic	PTC Czech s.r.o, Prague	C 230 (scan)	3 gantries, 1 horizontal	2012
France	CAL, Nice	CI65	1 horizontal	1991
France	CPQ, Orsay	S 250	1 gantry, 2 horizontal	1991
Germany	HZB, Berlin	C 250	1 horizontal	1998
Germany	RPTC, Munich	C 250 (scan)	4 gantries, 1 horizontal	2009
Germany	HIT, Heidelberg	S 250 (scan)	2 horizontal, 1 gantry	2009, 2012
Germany	WPE, Essen	C 230 (scan)	4 gantries, 1 horizontal	2013
Germany	PTC, Uniklinikum Dresden	C 230 (scan)	1 gantry	2014
Germany	MIT, Marburg	S 250 (scan)	3 horizontal, 1 45 degrees	2015
Italy	INFN-LNS, Catania	C 60	1 horizontal	2002
Italy	CNAO, Pavia	S 250	3 horizontal, 1 vertical	2011
Italy	APSS, Trento	C 230 (scan)	2 gantries, 1 horizontal	2014
Poland	IFJ PAN, Krakow	C 60	1 horizontal	2011
Russia	ITEP, Moscow	S 250	1 horizontal	1969
Russia	St. Petersburg	S 1000	1 horizontal	1975
Russia	JINR 2, Dubna	C 200	1 horizontal	1999
Sweden	The Skandion Clinic, Uppsala	C 230 (scan)	2 gantries	2015
Switzerland	CPT, PSI, Villigen	C 250 (scan)	2 gantries, 1 horizontal	1984, 1996, 2013
United Kingdom	Clatterbridge	C 62	1 horizontal	1989

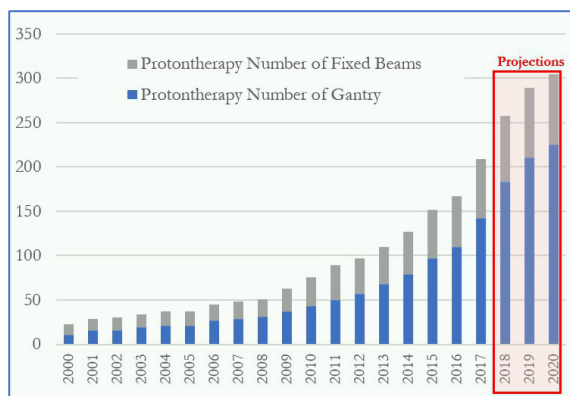


Figure 29: Protontherapy centres in Europe (left), number of beams and gantries in the world (above)

For the time being, proton therapy remains an expensive type of treatment, used for a limited number of indications (*with a strong proven experience in paediatric oncology*). However, given the global trend towards proton therapy, EU-28 MS cannot stay behind and should launch initiatives aimed at broadening clinical indications and possibly supporting research and investment.

Other forms of particle therapy are being studied, including carbon ions; helium, oxygen and argon ions, p-ions and antiprotons; fast neutron therapy; boron-neutron capture therapy, etc.

The primary challenge for proton therapy and other ion therapies is to prove their efficacy compared to other therapies for broader clinical-indication ranges. Systematic studies of RBE and related work could justify the higher cost of such treatments, leading to expanding the commercial demand for products. Equipment manufacturers must reduce costs to allow their adoption at smaller hospital centres. The inclusion of improved imaging as part of a treatment plan is also an important research topic for future facilities. Multidisciplinary research in radiobiology, machine learning, big data, and automation is needed to progress in radiotherapy.

The EC should support these initiatives, including studies and clinical trials aimed at broadening the clinical indications for proton therapy, for instance.

6.4. Molecular-targeted therapy (Nuclear Medicine) challenges

More details on radionuclide imaging can be found in Appendix A.10

Radionuclides (radioactive isotopes) have been employed in medicine ever since radioactivity was discovered. Produced in an accelerator or a nuclear reactor, the variety of radionuclides that can be used for in-vivo imaging and therapy suited to treating specific diseases, is increasing. Since the administration of radionuclides is minimally invasive and the duration of treatment is shorter than chemotherapy, targeted radionuclide therapy may become one of the most preferred types of cancer therapy. Given the potential radionuclides may offer for decisive breakthroughs in personalised medicine, clinical-application developments should be supported and the corresponding supply chain in Europe secured.

6.4.1. Current use of radionuclides

Radionuclides have two main uses in nuclear medicine: imaging and therapy.

For imaging, a pharmaceutical compound comprising a radionuclide ("labelled" with a radionuclide) designed to target the zone to be investigated is injected. The decay products of the radionuclide are detected and used to determine the location of each decay event, from which an image can be reconstructed.

The most commonly used imaging techniques are (see Eurostat data below):

- single-photon emission computed tomography (SPECT), today mostly using Tc-99m (daughter radioisotope of Mo-99), in which the radionuclide decays via the emission of a single gamma-ray photon that is then detected by a gamma-camera. SPECT procedure numbers have been quite stable in the EU-28 over the past few years.
- positron emission tomography (PET), mostly using F-18, in which the decay results in the emission of a positron (positively charged electron). The positron annihilates a nearby (negative) electron to release two gamma-rays, which are detected.
- PET Procedures have grown continually in the last few years. However, the major obstacle to SPECT Tc-99m substitution with PET is its cost. For economic reasons, Tc-99m SPECT use should remain high in the future as long as alternatives remain more expensive.

PET and SPECT are effective at detecting tumours and metastases and mapping the function of major organs such as the brain, where they can visualise physical changes associated with neurological disorders. SPECT and PET are very good at identifying the location of tumours, for example, but much worse at showing the surroundings. This is because the radiopharmaceuticals used are designed to deliver their payload to the highly-active tumour cells. To overcome this problem, SPECT and PET are now increasingly performed in combination with another imaging technique such as CT or MRI. These show the surroundings much better, thus giving a superior, combined picture of the tumour.

On the therapy side, however, despite I-131 being used since the World War II to treat hyperthyroidism and thyroid cancer, only limited progress has been made. The first therapeutic “best-selling drug”, Bayer’s Xofigo®¹⁵⁶ obtained its market approval in Europe and the USA in 2013 only and in Japan in 2016, and large developments are anticipated in the therapeutic field (see Chapter 5.1.3).

Indeed, Nuclear Medicine “theranostics” seems to pave the way for an effective “personalized medicine”. Nuclear medicine “theranostics”¹⁵⁷ consists of:

- binding an imaging radionuclide (the imaging “payload”) to a molecule (antibody, protein, etc., i.e. the “vector”) that specifically targets a tumour cell and injecting the compound into the patient. This allows accurate screening of the patient, precise characterization of the tumour and evaluating the appropriateness of the treatment using innocuous doses;
- then, labelling the “vector” with a radioisotope¹⁵⁸ that emits radiation that can destroy the tumour (the “treatment payload”), and injecting this therapeutic compound into the patient
- a final scan of the patient using the imaging compound allows checking the results, stopping, resuming or adapting the treatment.

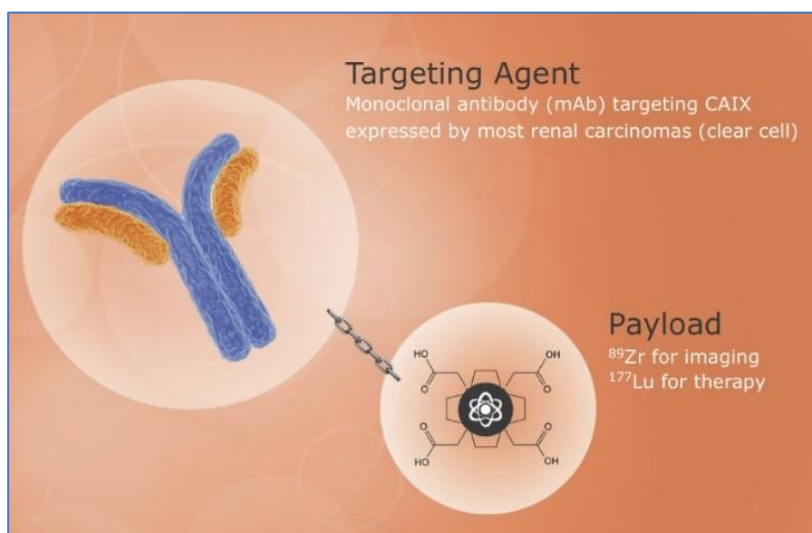


Figure 30: Theranostics example, Source - Telix

Such an approach would avoid successive trials calling for heavy oncology protocols until the appropriate one is effective for a given patient. In addition, the NM treatments could be administered in ambulatory care, with simple injections. As a result, better cancer treatment successes as well as potential costs savings for Health systems could be put into perspective.

However, radiotherapeutics and theranostics development presents two main challenges:

- the cost of development of new imaging radiopharmaceuticals;
- the availability of a sustainable supply chain for theranostics radioisotopes.

¹⁵⁶ Based on Ra-223

¹⁵⁷ Theranostics (or sometimes theragnostics) = Diagnostics + Therapy

¹⁵⁸ For therapy, radionuclides that decay into highly-ionising particles – alpha particles (helium nuclei) or high-energy beta particles (electrons) – which are capable of killing cancer cells are used.

6.4.2. The need for new imaging compounds

The key to developing theranostics is to find the right “vectors” to target cancerous tumours, which are able to bind successfully with an “imaging radioisotope payload” and a “treatment radioisotope payload”.

Whereas therapy radiopharmaceuticals are highly attractive for pharmaceutical companies, imaging compounds are far less attractive. The costs of developing an imaging agent are typically \$100–\$200 million over 8–10 years, compared to therapeutic drugs, for which costs amount to US\$ 800–US\$ 1,700 million over 10–12 years. Such time intervals and costs are due to the research phase and to Phase I-II-III trials, for both imaging and therapeutic agents. However, in contrast to the multibillion-dollar annual sales of a best-selling therapeutic drug, the annual sales of a best-selling imaging agent are in the \$400 million range. Hence, most imaging agents are living off their old success stories. The current prices for an imaging agent will not support developing a new drug unless it is used extensively.

The lack of any new imaging vector-payload combinations broadening clinical indications for NM hinders the development of theranostics. One solution may be “in-house” labelling. Under this approach, public institutions like hospitals, medical schools and laboratories, could be allowed to develop “in-house” labelled imaging compounds, with more “liberal” rules than for conventional drug development, especially in terms of Phase I trials, until commercial companies can take over the Phase II-III trials, hence reducing research-phase costs, while stimulating clinical research. Such a process would not preclude “GMP¹⁵⁹-like” requirements.

Moreover, radiotherapeutic development requires that a number of stakeholders work closely together: irradiators and processors, researchers, universities and labs, imaging equipment manufacturers, financiers, large pharmaceutical companies, etc.

6.4.3. The need for a sustainable supply chain

More details on the Radioisotope supply chain can be found in Appendix A.11, along with Economic Assessment of Tc-99m supply chain in Appendix A.12 and the Mo99/Tc99m supply and demand in Appendix A.13

Attracting the large pharmaceutical companies is key for developing Nuclear Medicine. To this end, radiopharmaceuticals market perspectives must be global. Translated into the supply chain, this provision means that mass-production of the coupled vectors and payloads must be possible, secured, cost-optimized and high quality (GMP), as well as versatile¹⁶⁰ particularly as concerns the radioisotope-production portion of the supply chain. This raises the challenge of securing the production means to produce radioisotopes in Europe.

The main radioisotopes necessary for imaging and therapy are listed below along with their preferred production means.

¹⁵⁹GMP: « good manufacturing practices ».

¹⁶⁰ able to produce the diverse isotopes on demand.

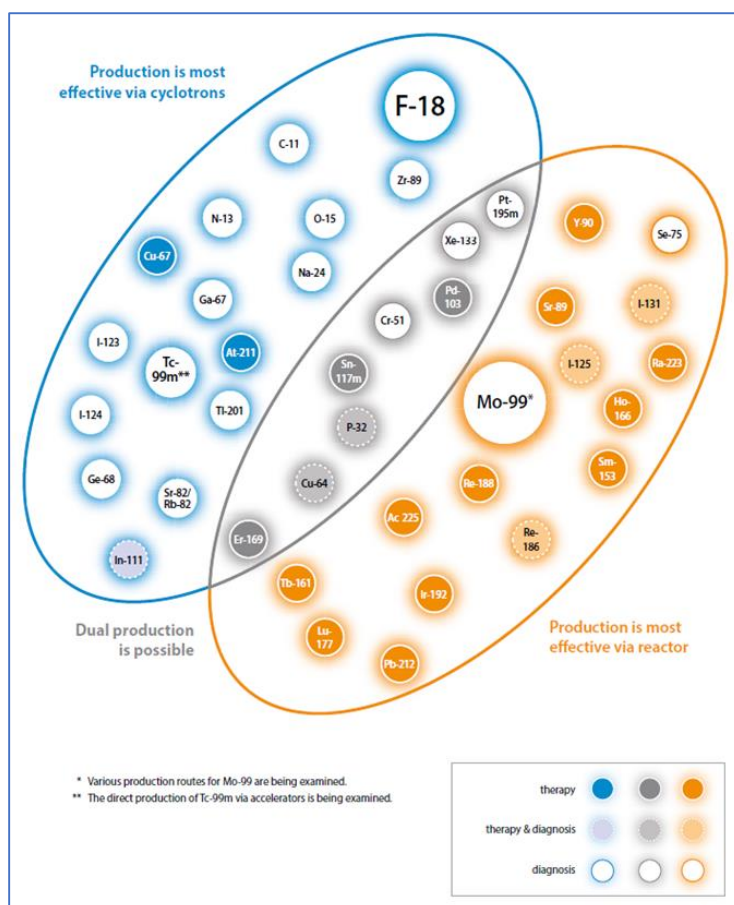


Figure 31 : Main medical radioisotopes production process

The main imaging radioisotopes are today produced efficiently in reactors (Mo-99/Tc-99m for SPECT) or cyclotrons (F-18 for PET, and probably Ga-68 in the near future¹⁶¹). However, the main therapeutic radioisotopes (*Ra-223*, *Sc-47*, *Y-90*, *I-131*, *Ho-166*, *Lu-177*, *Re-188*, *Bi-213*, *Ac-225*, *Pb-212*, etc.) or brachytherapy compounds (*Ir-192*, *I-125*, *Co-60*) are only or at best produced in research reactors. While a reactor is versatile enough to mass-produce all necessary radioisotopes simultaneously under the required GMP conditions, it is not the case for cyclotrons.

For Mo-99, as well as for the new radiotherapeutics, securing a cost-efficient, high-quality and mass supply of all the necessary radioisotopes in Europe is essential to avoid EU-dependence on foreign supplies. This raises the question of the sustainability of Research-reactor production of radioisotopes in Europe.

European Research Reactors, among them HFR (The Netherlands), BR2 (Belgium), Maria (Poland) and LVR-15 (Czech Republic) are producing about 60% of global needs for Mo-99 for SPECT imaging, which is the imaging workhorse (*>80% of the annual 10 million nuclear medicine imaging procedures in Europe*) and for the time being the main¹⁶² radioisotope produced in the reactors. Despite the increase in PET imaging, SPECT Mo-99 radioisotope imaging is rather stable or slightly declining in MS such as France and Germany (about 30% of EU procedures). Despite the lack of reliable EU-28-wide and global figures, there is no sign that the massive use of Mo-99 will decline in the near

¹⁶¹ Radioisotope currently subject to extensive studies.

¹⁶² In terms of volume and monetary value.

future. Its use could even increase if radiotherapeutics develop strongly, in line with predictions.

Only a dedicated multi-radioisotope-production reactor can allow a cost-effective, GMP proven, reliable, versatile and mass-production supply chain of all needed radioisotopes. Most of the European reactors are now encountering ageing problems. They are carefully monitored and audited, and are periodically subject to revamping operations in order to ensure their continued safe use, but their life cannot be extended indefinitely, hence jeopardizing the mass supply of radioisotopes. The OECD NEA¹⁶³ and the European Observatory on the Supply of Medical Radioisotopes¹⁶⁴ have been warning decision-makers for several years about the potential risks of a global shortage of medical radioisotopes.

In addition, the supply chain for radioisotopes should be secured right through to the supply of low enriched uranium (LEU) for irradiation targets and for reactor fuel. Even if LEU irradiation targets lead to increased radioisotopes costs and radioactive waste, they are preferred over highly-enriched uranium (HEU), the use of which raises nuclear security and proliferation concerns. For the time being, HEU continues to be used in Europe for certain radioisotopes production targets (but the last main supplier using HEU targets plans to switch to LEU in a near future) and as fuel for BR2 (conversion to LEU planned by 2026). Neither HEU nor LEU are produced in the EU-28. The secure supply of medical radioisotopes depends on securing an adequate supply of HEU and LEU required for their production. The question of LEU supply has been studied by an ESA Advisory Committee and its report is being updated.

As LEU targets tend to increase costs along the supply chain for Mo-99 production, it creates competition imbalances among EU players, whether or not they have already switched from HEU to LEU targets. EU could work with national authorities in order to enforce the systematic use of LEU targets in the EU-28.

A number of projects in the US and Canada are exploring alternative ways of producing radioisotopes. The US DOE sponsored different projects in the USA through direct financing. However, it seems that there is still a long way to go before the USA achieves self-reliance considering the maturity status of the various US projects (see appendix 14).

In any event, were countries like the USA to implement voluntary approaches and publicly invest in order to gain domestic-supply capabilities, the EU-28 should remain self-reliant on such strategic issues, which are essential for both European healthcare and economic growth, and not be placed at risk as was the case in 2008-2009.

¹⁶³ <https://www.oecd-neo.org/med-radio/>

¹⁶⁴ http://ec.europa.eu/euratom/observatory_radioisotopes.html

6.4.4. Nuclear medicine: Recommendations

With regard to the potential of Nuclear Medicine, obstacles to its development should be addressed. Such actions are primarily the role of professional organizations like the EANM in Europe or the SNMMI in the USA but may also require support from public authorities.

The SNMMI¹⁶⁵ Strategic Plan (see appendix 18) has the merit of exhaustively listing such obstacles¹⁶⁶, all of which are gaps to be filled. Transposed to Europe, initiatives where public support may be particularly useful are examined briefly below:

- In the regulatory domain: increasing the development and dissemination of clinical guidance documents, including appropriate utilisation criteria. Improving understanding among those developing new radiotracers and radiotherapeutics about the type of evidence needed by the EMA and domestic Market Authorities to approve them as safe, effective, reasonable and necessary. Communicate with National Market authorities and EMA for regulatory approval of emerging agents that are safe and effective. Consistently communicate about initiatives conducted in the field with legislative and regulatory bodies to promote greater understanding and support of NM/MI work.
- Ensuring adequate and appropriate reimbursement for NM/MI procedures by Healthcare reimbursement systems. Reimbursement practices are what really drives under/over-utilisation and these are the most direct way to change medical practice.
- In the educational domain: increasing the reserve and renewal of qualified personnel (practitioners, medical physicists, technologists, radiopharmacists, etc.) to practice nuclear medicine. Increasing awareness of NM/MI as an appealing and rewarding field for students interested in STEM careers.
- For the public: promoting greater understanding of radiation levels and benefits among the general public and in the medical field.
- In the supply chain domain: seeking improvements to ensure the integrity of the radioisotope supply chain and components; continuing to recommend full cost recovery even if this is difficult.
- In the research domain: encouraging and promoting research in the field.

An opportunity for NM European Research Centre(s)?

Large Research Infrastructure and Research programmes supported by the EC and the MS are key for maintaining the EU's prominent global position, attracting and developing innovative skills and new technologies. Europe relies on a very strong research foundation in accelerators and neutron-based research. Many European organizations work in this area. Major analytical facilities and campuses exist in Europe¹⁶⁷, which serve as reference hubs for various research activities and open innovation hubs for services

¹⁶⁵ Society for Nuclear Medicine and Molecular Imaging (USA).

¹⁶⁶ EANM has the same kind of analyses. Examining the US situation in detail is particularly useful, given the fact that the USA is at the forefront in terms of Nuclear Medicine procedures.

¹⁶⁷ Such as Harwell (ISIS, DIAMOND and CLF), Saclay (LLB and SOLEIL), Hamburg (EUXFEL, PETRA III and FLASH), Grenoble (ESRF, ILL and EMBL), PSI at Villigen (SINQ, SLS and SwissFEL), Trieste (Elettra, FERMI@Elettra and ICTP), Lund (ESS and MAX-IV) among many others, and the future ITER.

and industrial development. They help strengthen the links between Research Infrastructure, higher education and research institutions with a range of economic players, including industry, services and utilities. The internationally competitive environment and continual rotation of visitors and users at these hubs create a unique potential for training young researchers, technicians, managers and advanced-technology developers. They also favour political and public outreach.

The ESFRI (European Strategy Forum on Research Infrastructure) is a major EU tool in the policy-making process and for reaching decisions regarding research infrastructure in Europe to strengthen the European Research Area (ERA), and regularly updates its roadmap. ESFRI Projects and ESFRI Landmarks may access financing from the EU (Horizon 2020, ESIF, EFSI, etc.). In the ESFRI 2016 Roadmap, a series of projects concerning the ionizing-radiation sector are included, but Nuclear Medicine is not addressed per se.

Although some initiatives exist in Europe for Nuclear Medicine, hinging around FRM II in Germany, BR2 in Belgium, or HFR in the Netherlands, as well as within diverse European Medical schools and universities, it does not appear that such initiatives have yet reached the level of the large European campuses concentrated on accelerator and neutron sciences. The opportunity of founding European centre(s) of excellence, constituted around new means of radioisotope production and bringing together all the essential stakeholders required to establish efficient development of NM imaging and therapy compounds should be studied.

The potential interest in Nuclear Medicine therapy is currently poorly quantified, both in terms of health improvement and in terms of economic impact on the Healthcare systems. It now seems opportune and urgent to launch a thorough Health Technology Assessment to examine emerging therapeutic applications in Nuclear Medicine. Progressing in this direction and convincing decision-makers in this respect is recommended.

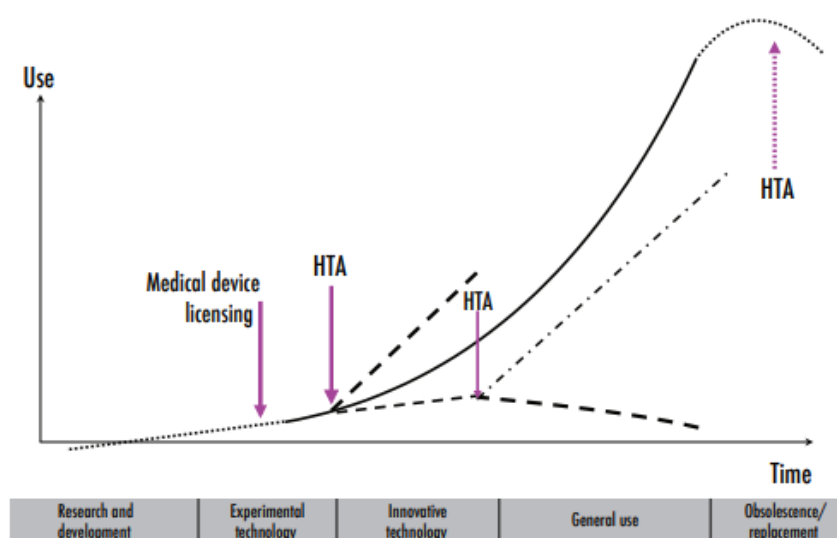


Figure 32: Health technology assessment and dissemination of health technologies¹⁶⁸

¹⁶⁸ Source: WHO

7. Industrial & Research challenges

More details on Industrial and research-application developments can be found in Appendix A.15

7.1. Diversity and potential of industrial applications

Ionizing radiation in the form of γ -rays, ions and energetic electrons or X-rays are tools used in a broad range of practical industrial applications and in applied research as shown below.

Radiation technologies Applications			
E Beams	Very low energy (surface treatments and processing) (less than 330 keV)	DETECTION	all analytical methods using electrons or X-rays (scanning electron microscopy, transmission electron microscopy, Auger electron spectroscopy, X-ray photoelectron spectroscopy and computer-aided tomography)
		Cutting, linking and pasting at the molecular level	Sterilization Seed treatment Disinfection of grains, nuts and spices 2D printing (food packaging) 3D printing Lacquering and coating Grafting
		Heating and local surface modification and drilling	melting, evaporation, welding, joining, drilling, hardening, diffusion, sintering, ...
	Low energy (changes in the bulk material) (330 keV to 10 MeV).	Polymer modification	Cross-linking of polymers (fi wires and cable insulation) for heat and abrasion resistance Pre-vulcanisation of components of car tyres (92% of all tyres)
		Materials processing	Colouring gemstones Semiconductor modification
		Sterilisation	50% per cent of single-use medical devices (such as syringes and scalpels) in the UK, and 40 to 50% of all disposable medical products manufactured in North America are sterilised by ionising radiation
		Environmental applications	Flue-gas treatment
			Treatment of waste-water and sewage
			Environmental remediation of hydrocarbon contaminated soils
			Conversion of fossil fuels
			Asphalt treatment
		Synergistic effects of technological developments in EB accelerators	Superconducting wind generators Magnetic separation Electrical grid technologies
		Special applications regarding biological hazards	Conservation of books, archives and artefacts Security
Ion beams	ION BEAM ANALYSIS	ENVIRONMENT (Air pollution) and CULTURAL HERITAGE	› Elastic or Rutherford backscattering (EBS or RBS), and also nuclear reaction analysis (NRA); › Particle-induced X-ray emission (PIXE), with an X-ray detector; › Particle-induced gamma-ray emission (PIGE), with a gamma detector; › Elastic recoil detection analysis (ERDA) with a particle detector at a forward recoil/scattering angle
	ION IMPLANTATION	Semiconductor industry	
		Proton-beam writing	
		Nuclear industry	emulate the effects of neutron damage
		Nanomaterials	
		Polymers	

Radiation technologies Applications			
RADIONUCLIDES based INDUSTRIAL RADIOGRAPHY (sealed or non-sealed sources)	X-Rays :	- Radiotracers : X-Rays from radioactive elements may be immersed in process streams, to detect (fluoroscopy) iron, nickel, copper, zinc, tin, lead, ...	- Linacs inspections (see security below)
	γ-Rays :	sealed sources, best for remote areas : ash content of coal on conveyor belt or on-line, weld/piping analysis. Non-destructive testing. Gauging applications (Well logging/moisture gauges, Level, Density, thickness gauges). Instrument calibration	The global gamma radioactive sources market for NDT applications is segmented mainly by sources into Iridium-192, Selenium-75, and Cobalt-60 . TOFD US : alternative technology (see http://www.cofrend.com/contrôles-non-destructifs/methodes-de-contrôle/ultrasons-ut/le-tofd/)
	Neutrons	- Thermal neutron capture : Cf-252 sources + sodium iodide detectors - (fast) Neutron inelastic scattering : Am-Be-241 sources + bismuth-germanate detectors (also sensitive to TNC). NIS used for on-line and on-belt controls in	
BORDER SECURITY	X-RAY IMAGING	Marine freight	
		Air freight	
		Rail cargo	
		People and mail	
NUCLEAR SECURITY	USE OF NEUTRONS		
	GAMMA-RAYS		
	SUPPORT TO MAINTAINING INTERNATIONAL TREATIES, SAFEGUARDS AND NUCLEAR ARMS CONTROL		
PHOTON SOURCES	SUPPORT TO STOCKPILE STEWARDSHIP		
	SYNCHROTRON-BASED LIGHT SOURCES (SRS)	› chemistry including subjects of interest to industry such as catalysts and batteries;	
	LINAC-BASED LIGHT SOURCES - FEL (fi XFEL) - ERL (Energy recovery Linacs)	› biomedicine including drug design and molecular biology relevant to health; › materials science including foods, polymers and textiles;	
	COMPTON SOURCES	› nanotechnology, including nano-	
NEUTRONS SOURCES	Complementary applications of those above	Research reactors	ILL (FR), FRMII (GE)
		Europe's spallation sources	ISIS (UK), SINQ (CH), ESS (SW)
		COMPACT NEUTRON SOURCES (CNSS)	

Figure 33: Industrial landscape of non-power applications

Ionizing radiation can modify the physical, chemical and biological properties of materials on an industrial scale. Many γ-sources, electron and ion accelerators have been built and installed for these purposes over the past fifty years and the field is still expanding.

The major industrial use of ionizing radiation is ion implantation in the semi-conductor industry and the modification of polymer properties in a variety of industrial applications such as wire and cable insulation; tyre manufacturing (92% of tyres are pre-vulcanized this way); the production of polymeric foams, hydrogels, heat-shrinkable films and tubing; and curing of coatings, adhesives and composites.

Ionizing radiation became a perfect tool for the synthesis and formation of nanoparticles and nanocomposites.

Sterilization by ionizing radiation accounts for the preparation of approximately 50% of single-use medical devices in the UK and 40–50% of all disposable medical products in North America.

Radiation technologies may also be applied to environmental protection or to cultural-heritage preservation. Efficient radiation technologies used for gas, liquid and solid-radioactive waste treatment exist to reduce environmental degradation. Cultural-heritage artefacts made of paper, textiles or wood are prone to microbial assault and their disinfection using ionizing radiation has been successfully demonstrated.

Another field of applications is based on ionizing radiation's penetration properties and the precision with which it can be detected using open and sealed radiation sources.

Optimization of industrial processes is essential, not only for efficient, safe and sustainable operations, but also to save materials and energy, to protect the environment and to reduce plant downtime. Complex industrial processes include environment-related processes (at harbours and dams, oil fields and ore/coal mines, for instance), so it is essential to have suitable means to investigate them for process optimization and trouble-shooting — preferably without shutting down the plant or process. Radiotracers and sealed-source techniques are the best-suited methods to address such problems. Automation and instrumentation and hardware improvements, such as tracer injection systems, detectors and data-acquisition systems are developed for safer reliable applications.

Neutron-beam irradiation is used for semiconductor doping, for material characterization via neutron-activation analysis and for complementary imaging to round out X-rays or γ rays.

Irradiation processes generally provide significant advantages compared to typical thermal and chemical processes, including higher throughput rates, reduced energy consumption, less environmental pollution, more-precise process control and products with superior qualities.

All these ionizing-radiation tools are based on science developed in universities and research centres and then transferred to industry to be used in a safe and appropriate manner.

The development potential of innovative industrial applications based on ionizing radiation tools is very large^{169,170,171,172,173}. Some examples should be highlighted:

- nanoparticles (NPs) and nanostructures manufactured with ionizing-radiation tools may be used in a number of areas, notably in Healthcare (see Box 1 below);
- the detection capabilities of ionizing-radiation tools, which are invaluable for any research lab, continue to be developed in other areas such as border or cargo security;
- food and seed sterilization (see Box 2 below);
- advanced manufacturing techniques (see Box 3 below);
- the environmental field could benefit from the unique properties of ionizing-radiation tools:

¹⁶⁹ See Nanoscale Radiation Engineering of Advanced materials for Potential Biomedical applications. IAEA Radiation Technology Report N°5.

¹⁷⁰ See the IAEA's International Conference on Applications of Radiation Science and Technology (ICARST 2017) proceedings.

¹⁷¹ See the 8th International Particle Accelerator Conference (IPAC 2017) proceedings.

¹⁷² See the APAE/EUCARD2 Final report, 2017.

¹⁷³ See the US DOE Workshop on Energy and Environmental Applications of Accelerators, 2015.

Applications of Electron Beam Technology	
Treatment of water and wastewater	Radiation processing to purify and decontaminate water
Treatment of flue gas	Radiation processing to purify gas streams
Treatment of sewage sludge	Radiation processing to decontaminate sewage sludge
Environmental remediation of hydrocarbon contaminated soils	Radiation processing of hydrocarbons to make contaminated soil more amenable to other remediation techniques
Medical waste sterilization	Radiation processing to decontaminate medical waste
Conversion of fossil fuels	Conversion of fossil fuels by radiation processing
Asphalt treatment	Improving wear-resistance and weather-resistance of asphalt via irradiation
Applications of Superconducting System	
Superconducting wind generators	More compact and efficient wind generators through use of superconductors
Magnetic separation	Separation in industrial flow streams with high magnetic fields
Electrical grid technologies	Superconducting power transmission and load- leveling

Figure 34: Electron beam and superconducting system applications

Box 1. Nanoparticles (NPs) and nanostructures

NPs and nanostructures are not entirely new, but the ability of humans to work, measure and manipulate at the nanoscale is. Radiation technologies have properties that are uniquely suited for the creation and characterization of new functional materials on the nanoscale. For example, low energy ion beams enable fabrication of three-dimensional structures, and high-energy ion beams are used for preparation of ion track membranes and nanowires. Membranes containing one to about 100 pores/cm² of highly uniform pore size are already commercially available. Using further modification, there are endless possibilities for creating track membranes with special properties and functions.

These membranes may be used as template materials for the synthesis of microstructures and nanostructures, in the form of wires or tubules. Magnetic, conducting and superconducting nanowires and nanotubes, single or in an array, have been manufactured in this way. These processes are being developed in France, Germany and Japan or the USA. The use of pulsed irradiation to synthesize polymer nanogels was initiated in Poland, and further developed in laboratories in Germany, Hungary and in an ever-increasing number of IAEA Member States. Properties of polymer nanogels, as compared to single macromolecules or non-cross-linked NPs include stability of shape and size, ability to react to external stimuli, ability to host small molecules and release them in a controlled way, ability to form non-flat, structured surfaces and stability against degradation. These properties make them potentially suited to healthcare applications, for example, in diagnostics as carriers of contrast agents or markers and in therapy as stimuli responsive coatings for drug or gene delivery, encapsulation and wound healing. These nanogels can be additionally functionalized by coupling with suitable biomolecules for targeting and imaging and can be used as additives to synovial fluids and intravenous drug carriers.

Nanoscale grafting of environmental sensitive hydrogel onto a surface of cell culture dishes (by γ or electron irradiation) enables harvesting of these cells by a change in the temperature or pH of the cell culture media. In this way cells can be harvested in a continuous sheet form. Such cell sheets overcome the limitations of conventional tissue engineering methods and have already shown good results in regenerative medical applications in Japan. Skin and corneal defects have been treated with transplantable cell sheets fabricated on these surfaces. Severe heart failure has also been treated with cell sheets fabricated from patients' own skeletal myoblasts. With further improvements of stimuli responsive culture, surface reconstruction of more complex tissues will be possible, leading to treatment of a wider range of diseases.

This process has generated interest in a number of IAEA Member States (Hungary, Italy, Poland, Turkey and USA among others), which are now exploring various routes for preparation of surfaces that are suitable for cell sheet engineering.

Box 2. Food sterilisation applications

Beyond the sterilisation applications in pharmaceuticals and smart packaging described above, ionizing radiation may also be used for food sterilization.

Seed treatment

Feeding the world's growing population is an enormous challenge, and an important aspect is ensuring that crop seeds are free from pathogens such as fungi, bacteria and viruses that can endanger health and food security. Seeds must be treated to kill these pathogens. However, the standard chemical seed dressing can result in the contamination of soil and ground water with waste products, the drifting of dressing agents across fields, and the killing of probiotic microorganisms. An alternative is the environmentally friendly, purely-physical disinfection of seeds using the biocidal effect of accelerated electrons. By precisely adjusting the energy of the e-beam, contamination on the seed surface can be treated without damaging the DNA of the seed grain.

The disinfection of grains, nuts and spices

Most credible estimates of the quantity of food wasted state that 20 to 30 per cent of food harvested never even reaches the first processing step, because it is lost to rotting and insect infestation. Treatment with e-beams can prevent this wastage. Using very low-energy e-beams, the disinfection effect is limited to the surface layer of the products where the infections are mainly located. This means that the bulk of the products stays untouched and therefore unchanged.

In addition, e-beam treatment is superior to other microbial inactivation technologies for the following reasons:

- > there is no change in taste (steaming and chemical treatment change the taste);
- > there is no change in texture (steam changes the texture, usually making the product unusable);
- > there is no change in colour;
- > there is no toxic residue;
- > the treatment can be designed as an in-line process, which is more efficient than a batch process,
- > the technology uses only one-tenth of the energy consumed by steaming;
- > it is scalable – compact, cost-efficient machines can be made for low-volume producers, and large, high-throughput machines can be designed for mass production.

There is substantial potential for e-beams in this application. Some key players in this business are based in Europe. The market for this technology has the potential of exceeding EUR 100 m over the next years and may have a positive impact on the

European economy.

However, the main limitation for food sterilisation is regulatory and the European legislation and regulations governing ionising radiation may seem obsolete. They do not differentiate between radiation that penetrates the entire volume of an object and radiation that stops at the surface, whereas both the FDA (US Food and Drug Administration) and the USDA (US Department of Agriculture) treat ionising radiation as an additive instead of a production process. The irradiation of food for disinfection is forbidden in most European countries, excluding herbs and spices. It is possible to obtain single-product approvals, but this is an expensive procedure. Furthermore, in most countries, virtually all food products that have been treated with ionising radiation must be labelled as such, which may deter producers and consumers.

Updating the regulations and laws governing the application of ionising radiation such that they address low-energy e-beams differently from radiation that penetrates the entire product could reduce food-borne illness, expand the world's food supply and ultimately make global food trade safer. It is recommended that the EC examines this opportunity.

Box 3. Additive manufacturing and structured sintering



Custom Cranio-Maxillofacial implant

In the field of additive manufacturing (AM), e-beam accelerators are currently used in a technology known as e-beam melting (EBM), which is able to produce metallic components with a high degree of complexity using computer-aided design (CAD) data. EBM is a powder-bed-fusion technology, by which high-density components are created by selectively melting this powder in a layer-by-layer fashion.

Current materials processed deploying EBM are mainly titanium-based alloys (Ti-6Al-4V, TiAl), which are used in the aerospace and medical-engineering industries. EBM systems are now installed in several countries across Europe with the main markets being the UK, Italy and Germany.

7.2. Overcoming challenges for further development

In order to disseminate the industrial potential of IR-based tools more widely, challenges must be overcome. As seen above, large Research Infrastructures and research programmes supported by the EC and the MS are key for maintaining the EU's prominent global position, attracting and developing skills and new technologies. Hence, industrial challenges are closely related to Research.

7.2.1. European Research tools

As pointed out in the Nuclear Illustrative programme¹⁷⁴, which covers both energy and non-energy applications, the EU must maintain its technological leadership in the nuclear

¹⁷⁴ COM(2017) 237 final.

field so as not to increase energy and technology dependence, and to provide European companies with business opportunities. This in turn will foster EU growth, jobs and competitiveness. Retaining technological leadership in the nuclear field is possible only if interested Member States maintain diverse and sufficiently-funded nuclear research capabilities, including education and training components. However, it will not be easy for Europe to retain leadership in all areas, which emphasises the importance of cooperation at European level. The ongoing Euratom programme contributes to these objectives by supporting nuclear research and training activities focused on continuous improvement of nuclear safety, security and radiation protection.

The EC is very active in the research field, supporting both research programmes and Research infrastructure (RI), notably with the Horizon 2020 initiatives^{175,176} under EU or Euratom regulations and the ESFRI 2016 Roadmap¹⁷⁷ with its updating process. The Horizon 2020 objectives, budgets, tools and programmes are listed in the table below.

¹⁷⁵Horizon 2020 and the Research Infrastructures Landscape. Version 0.1 17/02/2017.

¹⁷⁶Horizon 2020. Research Infrastructures offering free Access with EU support.

¹⁷⁷ STRATEGY REPORT ON RESEARCH INFRASTRUCTURES. Roadmap 2016. ESFRI.

H2020 Budget	M€	Comments
I Excellent science, of which:	24 441	
1. The European Research Council	13 095	
2. Future and Emerging Technologies	2 696	
3. Marie-Skłodowska-Curie Actions	6 162	
4. European research infrastructures	2 488	
II Industrial leadership, of which:	17 015	
1. Leadership in enabling and industrial technologies	13 557	
2. Access to risk finance	2 842	
3. Innovation in SMEs	616	
III Societal challenges, of which	29 678	
1. Health, demographic change and wellbeing;	7 472	
2. Food security, sustainable agriculture and forestry, marine	3 851	
3. Secure, clean and efficient energy	5 931	
4. Smart, green and integrated transport	6 339	
5. Climate action, environment resource efficiency and raw	3 081	
6. Europe in a changing world - Inclusive innovative and reflective	1 309	
7. Secure societies – Protecting freedom and security of Europe	1 695	
Science with and for society	462	
Spreading excellence and widening participation	816	
European Institute of Innovation and Technology (EIT)	2 711	
Non-nuclear direct actions of the JRC	1 903	
TOTAL EU REGULATION	77 028	

Fusion indirect actions	728	
Fission indirect actions	316	
Nuclear direct actions of the JRC	560	
TOTAL EURATOM REGULATION 2014- 2018	1 603	

1. Nuclear safety
1.1. Nuclear reactor safety,
1.2. Safety of nuclear fuels and fuel cycle,
1.2.a. Conventional nuclear fuels
1.2.b. Innovative nuclear fuels and fuel cycles
1.3. Radioactive waste management,
1.4. Nuclear Emergency Preparedness and Response (EP&R)
1.5. Environmental monitoring & radiation protection)
2. Nuclear security
2.1. Nuclear safeguards
2.2. Non-proliferation
2.3. Nuclear security and prevention of CBRN hazards)
3. Standards for Nuclear (Safety, Security and Safeguards),
4. Knowledge management, training and education
5. Non-energy applications of radionuclides and technologies

NFRP-2018-8	Radiation protection research (MEDIRAD, CONCERT (MELODI, EURADOS, ALLIANCE, NERIS)
NFRP-2018-9	Strategy for the exploitation of research results funded under Euratom Research and training Programmes in the field of radiation protection
NFRP-2018-4	Improved nuclear data for energy and non-energy modelling applications
NFRP-2018-6	European Joint Research Programme in the management and disposal of radioactive waste
NFRP-2018-7	Availability and use of research infrastructures for education, training and competence building
NFRP-2018-10	Encouraging innovation in nuclear safety for the benefit of European citizen

Table 16: Horizon 2020 budgets

H2020 in particular emphasizes dose effects and dose reduction, radioactive waste management and safety programmes, both under EU regulations and Euratom regulations, which are directly linked to issues associated with the ionizing radiation applications highlighted above in this document. More generally, the H2020 objectives, budgets and programmes represent a fully-comprehensive set of tools available to European companies, particularly SMEs (numerous in the Health field).

As concerns Research Infrastructure, the ESFRI (European Strategy Forum on Research Infrastructure) is on hand to help the EC in its policy-making process concerning research infrastructure in Europe so as to strengthen the European Research Area (ERA). ESFRI

Projects and ESFRI Landmarks may access EU tools listed above (Horizon 2020, ESIF, EFSI)¹⁷⁸.

A series of projects included in the ESFRI 2016 Roadmap are of direct or indirect concern to the ionizing-radiation sector, e.g.:

Name	Full name	Roadmap entry		Operation	Legal Status as of 03/2016	Capital value (M€)	Op. annual budget (M€/yr)
E-ELT	European Extremely Large Telescope	2006	2024*	Programme of ESO		1000	40
ELI	Extreme Light Infrastructure	2006	2018*	AISBL, 2013		850	90
				ERIC under preparation			
EMFL	European Magnetic Field Laboratory	2008	2014	AISBL, 2015		170	20
ESRF UPGRADES	Phase I	2006	2015	Programme of ESRF		180	82
	Phase II: Extremely Brilliant Source	2016	2022*			150	
ESS	European Spallation Source	2006	2025*	ERIC, 2015		1843	140
European XFEL	European X-Ray Free-Electron Laser Facility	2006	2017*	GmbH, 2009		1490	115
FAIR	Facility for Antiproton and Ion Research	2006	2022*	GmbH, 2010		1262	234
HL-LHC	High-Luminosity Large Hadron Collider	2016	2026*	Programme of CERN		1370	100
ILL 20/20	Institut Max von Laue-Paul Langevin	2006	2020*	Programme of ILL		171	92
SPIRAL2	Système de Production d'Ions Radioactifs en Ligne de 2e génération	2006	2016	Programme of Ganil		110	5-6
MYRRHA	Multi-purpose hYbrid Reactor for High-tech Applications	2010	2024*			NA	100
Euro-BioImaging	European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences	2008	2017*	ERIC under preparation		NA	1,55
E-RIHS	European Research Infrastructure for Heritage Science	2016	2022*			4	5
JHR	Jules Horowitz Reactor	2006	2020			1000	NA
ECRIN ERIC	European Clinical Research Infrastructure Network	2006	14	ERIC, 2013		1,5	2

The last two columns are 1) Construction costs and 2) Annual operating budget (M€/yr)

Figure 35: ESFRI roadmap associated projects

In order to explore whether or not EU Research efforts in the field of Ionizing radiation technologies are sufficient or not, the analysis can be conducted to cover the three technologies used in industry and research: accelerators, neutrons sources and radioisotopes.

7.2.2. Accelerator-based industrial and research challenges

The actual and potential use of accelerators, the diverse research programmes and tools and the needs in the accelerator domain have been extensively described in the EUCARD/APAE Final Report¹⁷⁹.

Accelerators already have a significant economic impact, but until recently, their expansion has been held back by the size and cost of the equipment. The accelerator

¹⁷⁸ See, for instance, the "Conclusions on the implementation of the roadmap of the European Strategy Forum on Research Infrastructure". Competitiveness Council Meeting Brussels, 26 May 2014.

¹⁷⁹ APAE Final Report. 2017

technologies must also operate in a complex environment with many government regulations and industrial constraints. Both the performance and economic competitiveness of these technologies will be critical for their successful adoption. In addition to these factors, other forces are at work, including the regulatory landscape, public perception of new technologies, and market incumbency of previous technologies.

Recently, compact low-cost, low energy e-beam accelerators have become available as industrialised products which leads to predict an “e-beam renaissance” with more very low-energy e-beam accelerators installed during the next 10 years than during their entire history of more than 50 years. Numerous countries are very active and Europe, which can rely on a long experience and unique network of scientists, labs, universities, massive research tools and industrial companies should not lag behind this renaissance. Hence, the basic impediments to deployment of accelerator-related technology should be addressed. The APAE/EUCARD2 Final Report details the actions to be taken at European level to develop accelerator-based applications for the greater benefit of the European community.

These actions are detailed in appendix 19 and summarized below.

APPLICATIONS OF ACCELERATORS IN EUROPE (APAE) / EUCARD2

Outcomes/Recommendations: Potential EC Actions

Develop Compact accelerators: More compact accelerator technology is a key factor in all applications. In this sense, the development, in the medium term, of superconducting components is crucial. In the longer term, laser and terahertz acceleration techniques could potentially offer a dramatic reduction in size, although significant development is still needed to establish if this reduction can be achieved in a suitable environment.

Improved designs and cost-effectiveness: Simpler and lower-cost designs and concepts, with higher efficiency, reliability, robustness, and reduced costs of operation are needed in many accelerator applications, more specifically in health, industry and security; even the ready mobility of accelerator equipment is a growing need for some applications.

Improved academia-industry interactions: The development of accelerators for “big science” drives the majority of advances in accelerator R&D worldwide. Manufacturers of accelerators for industrial and other uses are often not sufficiently interconnected in these efforts. Programmes are required to better interconnect commercial accelerator groups, research facilities, universities and health centres.

Improved student training and knowledge-transfer: Basic education and training of students in relevant fields are essential to increase the flow of a suitably trained workforce into industries manufacturing and applying accelerator technology; good knowledge-transfer into industry is also essential.

Improved public understanding of accelerators and their science: Investment in the better public understanding of the science and applications of accelerators is needed, as well as better-informed perceptions of any risks.

Improved R&D collaboration within the EU: A stronger coordination of R&D efforts and collaborations at EU level would be highly beneficial.

Further development of combined irradiation and imaging: The merging of irradiation techniques and online-imaging is a major step, especially in the health and security sectors, where rapid and accurate detection (and treatment in the case of health) are desirable.

No figures are available in the APAE report to quantify the costs of the identified gaps.

7.2.3. Neutron-based industrial and research challenges

Neutron scattering covers an extremely wide range of disciplines: from fundamental physics, through chemistry, materials, and biology, right through to interdisciplinary areas such as engineering and archaeology.

Neutron beams are versatile and irreplaceable tools that have a strong record of being used both to make scientific discoveries and to develop technology in a number of domains.

In Canada¹⁸⁰, for instance, in a call for a renewed infrastructure after the NRU shutdown, researchers give examples of research programmes, and among many others were:

- better storage of clean electricity (advanced batteries), enhancing renewables;
- manufacturing processes for light-weighting cars, ships and airplanes, or heat-treatment process optimization for car engine blocks;
- hydrogen storage and better fuel cells, materials that can capture CO₂, superconductivity;
- Neutron beams were at one time mainly applied to hard materials, but are now emerging as powerful and irreplaceable tools for the soft tissues of living things:
 - o Advanced-materials imaging techniques, including neutron imaging, are currently being developed to accelerate crop development;
 - o Research on the building blocks of living systems to determine their functions and how they interact is foundational. Neutron beams are uniquely powerful for studying cell membranes and biomolecules that interact with cell membranes, including cholesterol and vitamin E as well as proteins that play roles in cancer treatment or cardiac and neuronal disorders, yielding recent discoveries to better understand Parkinson's disease, human immunodeficiency virus (HIV), antibiotics and anaesthetics. Other recent neutron-beam projects have examined biomolecules that play roles in genetics, in the shelf life of drugs, and in factors that affect our bodies' ability to receive drugs. They have also recently been applied to cancer-fighting technology and to materials having the potential to reduce surgery recovery times.

¹⁸⁰ Neutrons for Materials Research. An Enabler of Clean Energy Technology. Canadian Neutron Beam Centre. October 2017.

Science at the Australian Centre for Neutron Scattering also covers many of these areas, with the main focus being on neutron-scattering strongholds: crystallography, soft condensed matter, solid-state physics, physical chemistry and, increasingly, biology.

Neutron sources complement the other technologies

According to the ESFRI Neutron Landscape Group, “many of the essential processes of life at the molecular level — and the pathological ways in which these are disrupted during illness — are also governed by complex, self-assembled or folded macromolecular structures. Advances in X-ray sources, free electron lasers, electron microscopy, NMR etc. will also hugely increase our understanding of such phenomena but, as is always the case, more answers also lead to new questions and, given the uniqueness of neutrons, the availability of more-intense neutron beams will ensure that neutron spectroscopy will play its part. All of these techniques, collectively and individually, are necessary to address the challenges of materials that face us in the 21st century.”

Neutron-source research requires investment.

Neutron beams are produced in research reactors. The USA, Japan, Korea, Australia and China have powerful neutron sources. According to the ESFRI Neutron Landscape Working Group¹⁸¹, there are shortcomings in the neutron-research field in Europe. In the words of Prof. Giorgio Rossi, Chair of the PSE Group and Chair-elect of ESFRI, “The ultimate scope of ESFRI is to provide a coherent and strategy-led approach to policy-making on Research Infrastructures to the Competitiveness Council of the EU. In the domain of neutron science and analytical facilities, the strategy-led approach must be urgently formulated as no individual ministerial authority or owner-consortium of the current infrastructures is in the position to address it”.

The European user community is the largest and most diverse in the world by far, numbering over 6,000 scientists and engineers from academia, national and international research laboratories and institutes, as well as from industry, all of whom use neutrons as an essential tool in an increasingly-wide range of research fields. Europe has led the field for ~40 years in scientific research using neutrons thanks to the broad versatile network of neutron sources in Europe. These include:

- the world’s two leading sources as measured by scientific output: the reactor-based Institut Laue Langevin (ILL) in Grenoble, and the accelerator-based ISIS facility near Oxford, with access available to the multi-disciplinary international scientific user community;
- as well as an array of high-quality medium flux facilities located in several different countries.

Relatively-modest investment is necessary to maintain this position. The next-generation neutron source for Europe — the European Spallation Source, or ESS — is now well under construction in Lund in southern Sweden. It promises not only to continue playing a flagship role in neutron scattering, but also to embrace exciting new opportunities.

However, by 2025, Europe will have only 4 or 5 functioning neutron sources, at best. Most probably these will come from ILL, FRM-II (MLZ), ISIS, SINQ& ESS. Highly

¹⁸¹ Neutron scattering facilities in Europe. Present status and future perspectives. ESFRI Physical Sciences and Engineering Strategy Working Group. Neutron Landscape Group. June 2016

productive and still-viable sources, such as LLB and BER-II, will already have ceased to operate. By the beginning of the 2030s a likely scenario — failing mitigating actions — is that Europe will find itself with the ESS and only one or two other neutron sources. This would lead to adverse consequences due to the instrument-days capacity available in Europe (see figure on left).

Consequently, a number of key action points are identified by the ESFRI's Neutron Landscape Group in the ESFRI Roadmap 2018, which a collective European strategy should address.

Shortcomings in the neutron-source field

Stressing the importance of neutron sources in a number of essential research domains and stating that the potential of “instrument-days”, which quantifies the “productivity” of the installations, are dramatically dropping in the future (see picture below), the Neutron Landscape Group of ESFRI has identified a series of challenges which a collective European strategy should address.

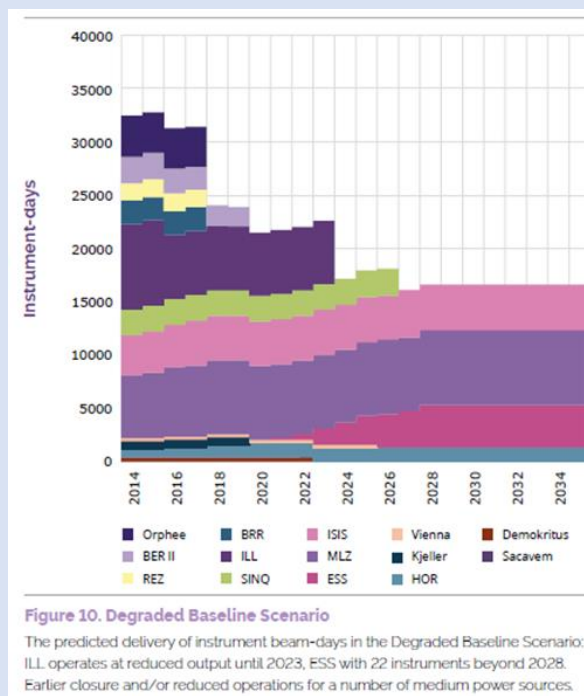


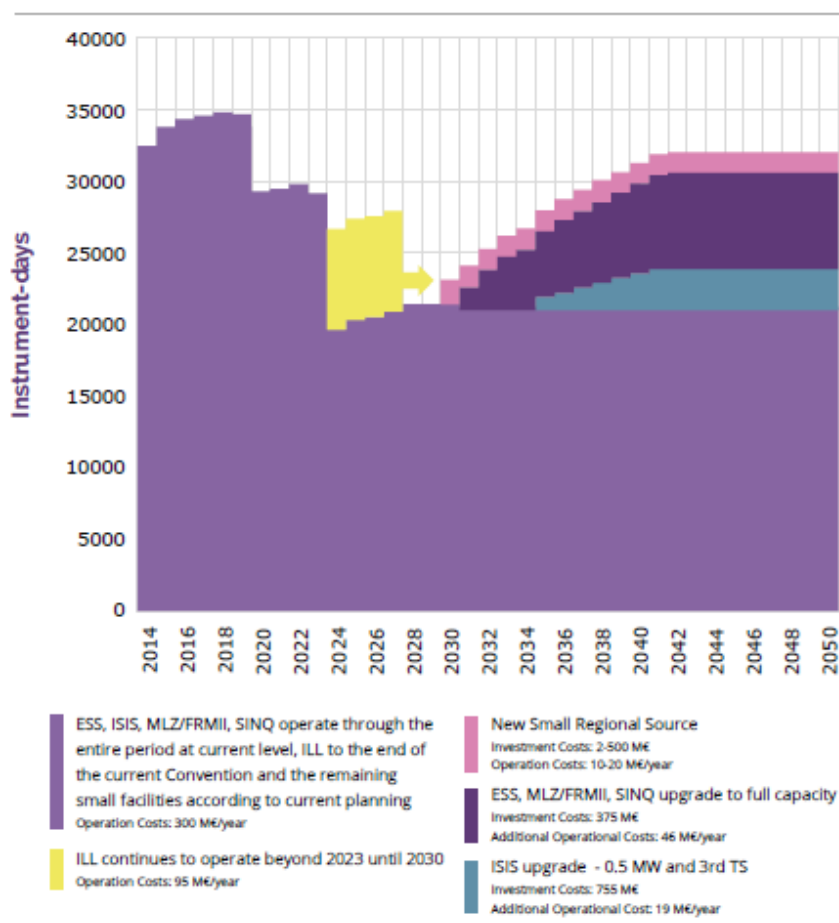
Figure 36 : European Neutron sources availability (degraded scenario)

The key action points are:

- Developing a growth plan for the ESS (European Spallation Source) without delay, which provides for more than the 22 planned instruments and committing secure funding in order to achieve this end;
- Examining the opportunities available to invest in the broad neutron pool in Europe: implementation of an upgrade programme for 4 to 5 of the newest current sources — ESS, ILL, ISIS, MLZ and PSI — that can be operated beyond 2030;
- Maintaining the ILL's (Institut Laue-Langevin) world-leading scientific output over an extended overlap period alongside the ESS by providing political and financial support;
- Launching studies for the development of new medium-power high brilliance neutron installations;

- Mobilizing the European neutron-user community such that they, in partnership with source facilities, launch proactive and cohesive efforts to secure the future robust health of the discipline;
- Exploring the feasibility of implementing a more coherent and coordinated strategy group at the pan-European level to oversee and sustain Europe's neutron sources at an appropriate level by adopting a collective position;
- Current sources are urged to examine their operating regimens and to reinvent themselves, implementing best practices from other disciplines;
- Developing an Open Access to Data policy and identifying mechanisms for neutron scattering, under a broader initiative to promote analytical methods in materials science;
- Launching a study on a next generation world-leading European neutron source that would begin to operate in the second half of the century; exploring possible global partnerships.

In its report, the ESFRI Neutron Landscape Group quantifies the diverse solutions possible for filling the identified gaps: upgrades, extensions and new facilities can be combined in a multitude of different ways. To be realistic however, the Group stresses that for any of these scenarios the discussion between funding agencies and sources needs to start now.



7.2.4. Radioisotope industrial and research challenges

The Healthcare component of radioisotope research mainly concerns Nuclear Medicine and has been addressed in section 6.4. In that section, the recommendation was to study the opportunity of creating a Nuclear medicine Research Centre based on the model of the large research infrastructures existing in the accelerator and the neutron fields described in the preceding paragraphs. In order to pave the way for such an initiative, a Health Technology Assessment of Nuclear medicine has been recommended.

Moreover, radioisotopes — in the form of radiation sources or radiotracers — are also tools used in a number of domains in other health, industry, agriculture or environmental applications and studies. The ICARST 2017¹⁸² proceedings confirms that research is underway in numerous areas such as advanced polymeric materials, ion exchange membranes, nanomaterials, waste treatment, sterilization, security/detection, cultural heritage preservation, industrial gauging and agriculture, or equipment such as the “table top” synchrotron. Statistically, most of papers presented at ICARST 2017 come from outside the EU. To which extent investment gaps exist in these fields in Europe should be assessed in a further study.

7.3. Radiation technologies and KETs

The present study has evidenced the diversity of Health, Industrial and Research applications of ionizing radiation tools. This diversity and the fact that these tools are often embedded into equipment and services where their specific value can hardly be isolated, making their economic impact difficult to evaluate reliably. However, their unique role for improving Health and for underpinning and enabling other technologies, products and services has been highlighted. A number of challenges remain to be overcome in order Europe can derive maximum benefits of IR-based tools in Health, Industry and Research.

To achieve that, a prerequisite is that the IR tools are considered as key applications.

The “key enabling technologies” in Europe are the subject of the corresponding High-Level Group Final Report, issued in 2015¹⁸³, and are introduced that way: *In his political guideline document for the new European Commission, President Juncker said that “[...] we need to maintain a strong and high performing industrial base [...]. To achieve this, we need to stimulate investment in new technologies [...]”. Commissioner Bieńkowska, in charge of Internal Market, Industry, Entrepreneurship and SMEs, stated “Together with the Commissioner for Research, Science and Innovation, I want to use the Horizon 2020 Programme and other EU policy instruments in order to support close to market industrial innovation and key enabling technologies”. Commissioner Moedas, in charge of Research, Science and Innovation, stated “We must prioritise commercialisation. Turning science into technology. Bringing technology to market”.*

The following five KETs were regarded as strategically the most relevant with regard to the general objective of European reindustrialization:

- NT (nanotechnology);
- MNE (micro- and Nano electronics, including semiconductors);

¹⁸² Programme and abstracts. International Conference on Applications of Radiation Science and Technology. ICARST 2017.

¹⁸³ HLG on Key Enabling Technologies. KETs : Time to act. Final Report. June 2015

- PHOT (photonics);
- AM (advanced materials);
- IB (biotechnology).

A sixth, more overarching, KET was added to include the manufacturing side of the industry: AMT (advanced manufacturing technologies).¹⁸⁴

The radiation-based technologies have not been retained as “key enabling technologies” by themselves, but it should be considered that, in addition of their uses per se, they provide powerful tools for supporting nanotechnology, nano-electronics, photonics, advanced material characterization, treatment or manufacturing and biotechnologies.

	Charged-particle beams (accelerators)	X-Rays	Radioisotopes (α , β , γ emitters)	Neutrons
All KETs	all radiation modalities used for material/biological properties investigations for all KETs			
IB (biotechnology).	Nuclear medicine, advanced imaging and therapy			
AM (advanced materials);	Material processing			
AMT (advanced manufacturing technologies)	Additive manufacturing	Quality control	Industrial gauging Quality control	Quality control
NT (nanotechnology);	Polymers cross-linking			
MNE (micro- and nanoelectronics)	Ion implantation EUV, VUV lithography	Metrology & Quality control		
PHOT (photonics);	Synchrotron, free electron lasers (FEL)			

Table 17: Relation between KETs and radiation technologies

In order to substantiate this contribution and convince the decision-makers about the decisive impact of ionizing radiation technologies on the KETs development, a further study should be launched to assess and quantify better the relations of these technologies with each of the above KET.

¹⁸⁴ Horizon 2020 : Key Enabling Technologies (KETs), Booster for European Leadership in the manufacturing sector. EC/DG for Internal Policies. 2014

8. Spent fuel and Radioactive waste challenges

Ionizing radiation presents major benefits for European Health, Industry and Research. However, they may raise wastes challenges.

8.1. Radioactive Waste overview

Radioactive waste volumes stemming from the non-energy sector

A detailed radioactive waste inventory by type of non-energy activity (Nuclear Medicine Imaging, Therapeutics, Industry, Radioactive item manufacturing, Consumer products, etc.) is generally not available for the EU-28 countries. The breakdown is usually limited to the Nuclear Industry, Fuel Cycle, Research and 'Other' (Industry, Health, etc.). An example of such detailed radioactive wastes inventory from non-power applications can be found at ANDRA (France). ANDRA collects currently over 3000 radioactive waste packages generated within the non-electronuclear sector each year, providing the following breakdown in 2016.

Categories of radioactive waste		Vol.
Solid waste	burnable waste	16 t
	non-burnable waste	11 t
	putrescible waste	2 t
Scintillation vials	/	17 t
Liquid Waste	solvents and oils	3 t
	liquid aqueous waste	25 t
Lightning rods	/	2.4 t
Salts/radium objects	/	3.4 t
Others	smoke detectors	165 kg
	sealed sources	470 kg
	health radium items	8 kg

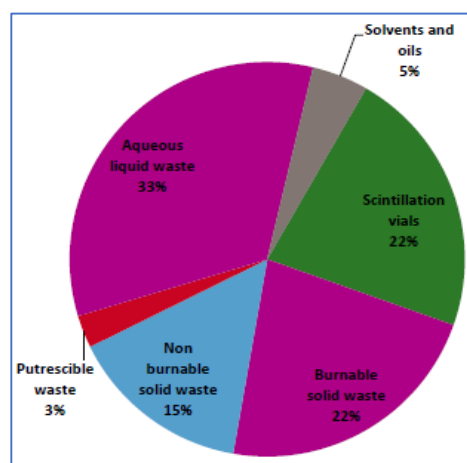


Figure 38: VLLW and I&LLW waste collected by ANDRA per year for non-power applications

These radioactive wastes come from roughly 400 different active producers (universities, laboratories, industry, etc.), while over 80% by volume of such radioactive wastes are from the Healthcare Sector. An average of 0.9 m3 of radioactive waste per production site per year can be accounted for.

According to the ANDRA¹⁸⁵, the main characteristics of the non-power sector are:

- Low volumes (in France, less than 80 tons per year in total), which are very variable in nature and radiological activity;
- Decreasing volumes (-4% per year on average) due to technology changes and market globalisation;
- Team turnover rates are high and workers frequently have no specialized training in radioactive waste management.

MS situation versus non-energy sector radioactive waste

Whether a Member State uses Nuclear Energy or not can lead to major differences in the Radioactive Waste status of the country. Indeed, given its volumes and activity (spent fuel), radioactive waste stemming from Nuclear Power Production largely impacts the

¹⁸⁵ European Conference on Addressing Societal Challenges Through Advancing the Medical, Industrial and Research Applications of Nuclear and Radiation – 20 & 21st March 2018

Radioactive Waste strategy of the country. The total VLLW & I&LLW non-electronuclear radioactive waste collected by the Radioactive Waste Agency (ANDRA) only represented a small fraction of total collected volumes (about 700,000 m³), for instance. Hence, two different typologies of countries must be distinguished, based on their utilization of ionizing-radiation applications:

1. Countries equipped with numerous Nuclear Power Plants (under activity, decommissioning or Nuclear Phase-out). These countries generally have considerable radioactive Waste Management Infrastructure due to their Nuclear Program (e.g. France, Germany, the United Kingdom) and actively search for long-term disposal solutions. In those countries, non-power application radioactive wastes represent a minor share of national radioactive wastes, hence they can benefit from existing infrastructures for nuclear power radioactive wastes.
2. Countries without Nuclear Energy or with a reduced number of NPP. Some of the non-power application radioactive wastes (*mainly High-Level Wastes and Intermediate Level Long Lived Waste*) may represent a major challenge for those countries, through the need of dedicated infrastructure for radioactive waste treatment, storage and disposal.

Radioactive Waste challenges

The radioactive waste challenges are different according to the nature of the waste, spent fuel, sources or VLLW:

- The challenge of spent fuel from Research Reactors (highly enriched Uranium) conditioning and disposal;
- The challenge of radioactive wastes generated by the radioisotope production supply chain, largely Mo-99;
- The challenges of disused sealed sources, with a focus of High Activity Sealed Sources (HASS);
- The challenges linked to other non-power applications, including cyclotrons, x-ray generators and accelerators as well as the tritium issue.

8.2. Spent Fuel from research reactors

The detailed list of EU-28 research reactors is given below, installations with core power inferior to 1 MW have been removed.

Country	Facility Name	Type	Thermal Power (kW)	Status
Austria	ASTRA	POOL	10000	DECOMMISSIONED
Belgium	BR-1	GRAPHITE	4000	OPERATIONAL
Belgium	BR-3	PWR POWER	40900	DECOMMISSIONED
Belgium	BR-2	TANK IN POOL	100000	OPERATIONAL
Bulgaria	IRT-Sofia	POOL, IRT	2000	PERMANENT SHUTDOWN
Czech Republic	LVR-15 Rež	TANK WWR	10000	OPERATIONAL
Denmark	DR-2	POOL	5000	DECOMMISSIONED
Denmark	DR-3	HEAVY WATER	10000	UNDER DECOMMISSIONING
France	EL-2	TANK	2500	DECOMMISSIONED
France	Triton	POOL	6500	DECOMMISSIONED
France	Melusine	POOL	8000	DECOMMISSIONED
France	Orphee	POOL	14000	OPERATIONAL
France	EL 3	HEAVY WATER	18000	DECOMMISSIONED
France	Cabri	POOL	25000	OPERATIONAL
France	Pegase	TANK	30000	PERMANENT SHUTDOWN
France	Siloe	POOL	35000	DECOMMISSIONED
France	Phebus	POOL	38000	UNDER DECOMMISSIONING
France	Rapsodie	FAST, POWER	40000	UNDER DECOMMISSIONING
France	G-1	GRAPHITE PILE	46000	UNDER DECOMMISSIONING
France	ILL High Flux Reactor	HEAVY WATER	58300	OPERATIONAL
France	Osiris	POOL	70000	UNDER DECOMMISSIONING
France	Scarabee	POOL	100000	DECOMMISSIONED
France	RNG New Generation	BWR-PROTOTYPE	120000	PERMANENT SHUTDOWN
France	EL 4	HEAVY WATER	267000	UNDER DECOMMISSIONING
France	PHENIX	FAST BREEDER	563000	UNDER DECOMMISSIONING
Germany	FMRB	POOL	1000	UNDER DECOMMISSIONING
Germany	FRN	TRIGA MARK III	1000	UNDER DECOMMISSIONING
Germany	FRF-2	TRIGA CONV	1000	DECOMMISSIONED
Germany	FRM	POOL	4000	UNDER DECOMMISSIONING
Germany	FRG-1	POOL	5000	UNDER DECOMMISSIONING
Germany	BER-II	POOL	10000	OPERATIONAL
Germany	RFR	TANK WWR	10000	UNDER DECOMMISSIONING
Germany	FRJ-1 (MERLIN)	POOL	10000	DECOMMISSIONED
Germany	FRG-2	POOL	15000	UNDER DECOMMISSIONING
Germany	FRM II	POOL	20000	OPERATIONAL
Germany	FRJ-2 (DIDO)	HEAVY WATER	23000	UNDER DECOMMISSIONING
Germany	NS Otto Hahn	PWR PROPULSION	38000	DECOMMISSIONED
Germany	FR-2	TANK	44000	UNDER DECOMMISSIONING
Greece	Demokritos (GRR-1)	POOL	5000	EXTENDED SHUTDOWN
Hungary	Budapest Research	TANK WWR	10000	OPERATIONAL
Italy	TRIGA RC-1	TRIGA MARK II	1000	OPERATIONAL
Italy	ISPRA-1	HEAVY WATER	5000	PERMANENT SHUTDOWN
Italy	Galileo Galilei RTS-	POOL	5000	DECOMMISSIONED
Italy	Avogadro RS-1	POOL, MTR	5000	DECOMMISSIONED
Latvia	SRR Salaspils Research	POOL	5000	UNDER DECOMMISSIONING
Netherlands	KSTR	AQUEOUS BREEDER	1000	DECOMMISSIONED
Netherlands	HOR	POOL	2300	OPERATIONAL
Netherlands	HFR	TANK IN POOL	45000	OPERATIONAL
Poland	EWA	TANK WWR	10000	UNDER DECOMMISSIONING
Poland	MARIA	POOL	30000	OPERATIONAL
Portugal	RPI	POOL	1000	PERMANENT SHUTDOWN
Romania	VVR-S Bucharest	TANK WWR	2000	UNDER DECOMMISSIONING
Romania	TRIGA II Pitesti - SS	TRIGA DUAL CORE	14000	OPERATIONAL
Spain	JEN-1 Mod	POOL	3000	DECOMMISSIONED
Sweden	R2-0	POOL	1000	UNDER DECOMMISSIONING
Sweden	R-2	TANK	50000	UNDER DECOMMISSIONING
United Kingdom	HERALD	POOL	5000	DECOMMISSIONED
United Kingdom	MERLIN	POOL	5000	DECOMMISSIONED
United Kingdom	BEPO	GRAPHITE, AIR	6500	UNDER DECOMMISSIONING
United Kingdom	Dragon	HE COOLED	20000	UNDER DECOMMISSIONING
United Kingdom	Dounreay MTR	HEAVY WATER	22500	DECOMMISSIONED
United Kingdom	DIDO	HEAVY WATER	26000	UNDER DECOMMISSIONING
United Kingdom	PLUTO	HEAVY WATER	26000	UNDER DECOMMISSIONING
United Kingdom	Dounreay Fast Reactor	FAST BREEDER	65000	UNDER DECOMMISSIONING
United Kingdom	Windscale AGR	GRAPHITE AGR	120000	DECOMMISSIONED

Table 18: EU-28 Research reactors (power > 1 MW)

A Research reactor is periodically refuelled with new fuel elements to replace the spent ones.

Yearly research-reactor fuel consumption among EU MS

As a first approximation, fuel consumption is proportional to total core power and the type of fuel. It should be noted that for very small cores, i.e. low total core power, the number of neutrons escaping from the core is higher and can lead to much higher fuel consumption depending on the design of the neutron reflector.

If we consider there are 250 days of operation per year on average, and a fuel consumption of 1.9 gU per MWd¹⁸⁶, the following yearly fuel consumption can be roughly estimated.

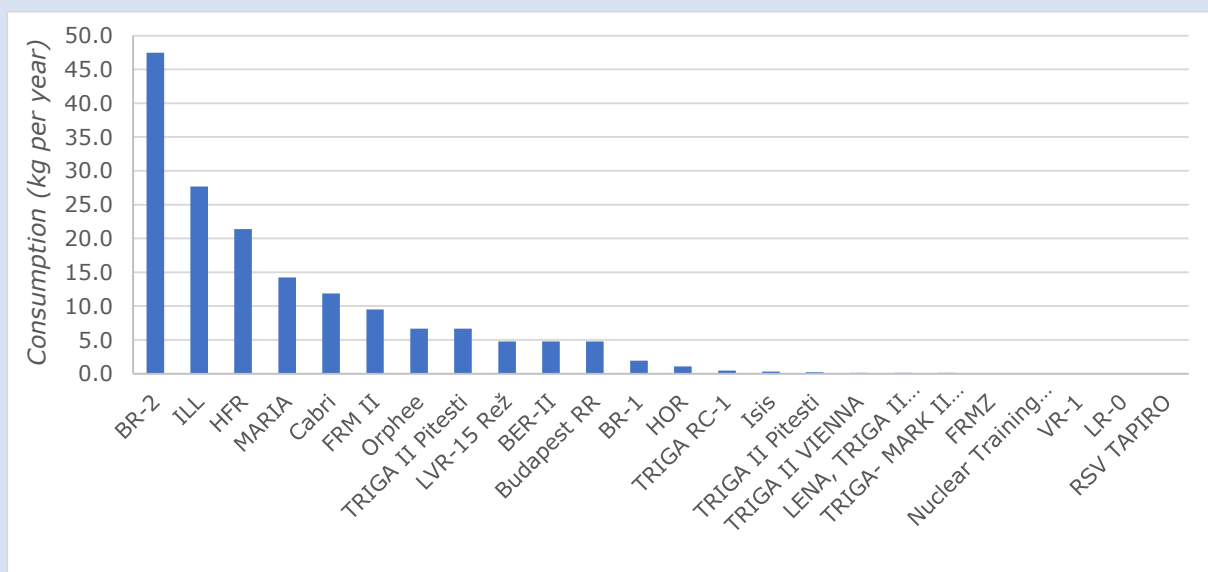


Figure 39: Rough evaluation of Yearly Fuel consumption by European Research Reactors - NucAdvisor

The direct correlation between the reactor's power output and average fuel consumption enables estimating the fuel consumption for current EU-28 reactors. Over 95% of European Union Research-Reactor fuel consumption results from less than 10 units.

Over the past few decades, highly-enriched Uranium (HEU) has been extensively used in various applications (e.g. deep-space propulsion, icebreaker propulsion), and particularly for Research Reactor Fuel and Radioisotope production. The basic function of research reactors is to provide a maximum number of neutrons for scientific, industrial, or medical applications. To this end, in research reactors where neutrons result from the fission process, the density of fissile nuclei in the fuel has to be maximized. Historically, this was accomplished through the use of highly enriched uranium (HEU). Motivated by non-proliferation objectives, international efforts¹⁸⁷ have been launched to progressively minimize and eventually abolish the use of Highly Enriched Uranium throughout the world.

¹⁸⁶ Estimate based on HFR (the Netherlands) and Osiris (France) fuel consumption, respectively 1.85 and 1.9gU/MWd

¹⁸⁷ GTRI RERTR (Global Threat Reduction Initiative/ Reduced enrichment for Research and Test Reactors) launched by US DOE 1978

The following table gives a HEU/LEU status summary for the main radioisotope production reactors in the EU:

Name	Country	Status	HEU Fuel	LEU Fuel
BR-2	Belgium	In Operation	From 1961	/
HFR	Netherlands	In Operation	1961-2006	From 2006
LVR-15	Czech Republic	In Operation	1957-2011	From 2011
MARIA	Poland	In Operation	1974-2015	From 2015
FRM-II	Germany	In Operation	From 2004	/
Triga 2 Pitesti	Romania	In Operation	1980-2006	From 2003
RJH	France	Under construction	From 2022	Conversion ASAP
OSIRIS	France	Def. Shutdown	1966 to 1995	1995 to 2015
PALLAS	Netherlands	Planned	/	From start
TRIGA-II	Austria	In Operation	Until 2012	Since 2012
GRR-1	Greece	Extended shutdown	Until 2005	From 2005
DR-1 to 3	Denmark	Under decom.	/	Until shutdown
RPI	Portugal	Permanent shutdown	Until 2008	From 2008

Table 19: Status of Main EU-28 Research Reactors regarding HEU/LEU

Despite the current use of LEU Fuel in the vast majority of Research Reactors in the EU, they all began their operations using HEU Fuel, which presents particular radioactive waste-management issues, including those of criticality and security.

The following section illustrates the differences among EU countries in terms of Spent Fuel Management strategies. Data stem from the National reports on compliance under the obligations of the Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management.

Belgium – BR-2

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
~1400 Fuel Assemblies	Yes (France, UK)	ONDRAF/NIRAS Belgoprocess	No solution but R&D

BR-2 Spent Fuel has been reprocessed in La Hague¹⁸⁸ (1172 Fuel Assemblies - AREVA NC – France) and by UKAEA (240 Fuel Assemblies - now DSRL – UK) where spent fuel has been down-blended to low enrichment by dilution with spent fuel from Belgium NPP Spent Fuel. Currently, radioactive wastes resulting from RR Spent Fuel reprocessing have been repatriated to Belgium and taken on by the ONDRAF/NIRAS. They are currently stored in the ONDRAF/NIRAS building 136 at Belgoprocess. No solution for the Final Disposal of these wastes currently exists at the moment in Belgium. R&D is being conducted at the ONDRAF/NIRAS on a Geological Repository based on the “super-container concept”¹⁸⁹. Research Reactor Spent Fuel Radioactive Wastes will benefit from Belgium’s nuclear programme radioactive waste infrastructure.

¹⁸⁸ <https://economie.fgov.be/sites/default/files/Files/Energy/National-programme-courtesy-translation.pdf>

¹⁸⁹ https://www.ensi.ch/de/wp-content/uploads/sites/2/2015/12/Beilage-06-Belgiums-supercontainer-concept-ONDRAF_05-11-2015.pdf

Germany – FRM-II

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
~190 Fuel Assemblies (2012) ¹⁹⁰	No	CASTOR MTR2 (onsite)	Not available

In Germany, the spent fuel of prototype and research reactors are stored in an interim storage facility for up to 40 years, inside CASTOR MTR2 multi-purpose casks, waiting for the availability of a geological repository. The substantial HLW volumes generated by the German Nuclear Programme should prompt future developments to deal with the geological disposal issues.

Poland – MARIA

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
~500 Fuel Assemblies ¹⁹¹	No	Pool + Dry Storage	No activities underway

MARIA Spent Fuel was first stored under water in away-from-reactor facilities. After Fuel corrosion came to light, a large programme of encapsulation was launched by authorities. “Long-term” storage under water (>20-30 years) was not initially foreseen, as Spent Fuel was initially supposed to be taken back by Russian Authorities (HEU Fuel Supplier). Between 2009-2016 all HEU Spent Fuel was finally sent back to Russia (under the GTRI RERTR programme). For LEU Fuel in use since 2015, interim storage will be accommodated in MARIA pools, then dry storage should be used. No long-term solution is currently foreseen in Poland, as future surface repositories will only accept low and intermediate level radioactive wastes. In addition, LEU will be provided by the USDOE and CERCA until 2017, after which Russia should become the new fuel supplier¹⁹² (*with agreement on fuel repatriation by Russia*). Spent fuel from Poland’s Research Reactors started to accumulate in 2015 and a long-term strategy remains to be defined.

Czech Republic – LVR-15

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
~170 Fuel Assemblies ¹⁹³	Yes (Russia)	HAW Storage Facility	Site Selection Process

In the Czech Republic, the interim storage solution is well defined: the HAW Storage Facility has been specifically designed for ÚJV Řež RAW and Spent Fuel. LEU Spent Fuel is currently stored inside the LVR-15 Reactor Pool (30 FA) and in an on-site Spent Fuel

¹⁹⁰ https://books.google.fr/books?id=V4roCQAAQBAJ&pg=PA177&lpg=PA177&dq=FRM-II+spent+fuel&source=bl&ots=Gg97C8UOVK&sig=UIHd54Erc_u-zJqvT_zM0k5O8aE&hl=fr&sa=X&ved=0ahUKEwicmo2b2MXXAhUCvBoKHbvXCLU4ChDoAQg4MAI#v=onepage&q=FRM-II%20spent%20fuel&f=false

¹⁹¹ National Report of the Republic of Poland in Compliance with the Obligations of the Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management - Poland’s 5th national report as referred to in Article 32 of the Joint Convention
<http://www.bip.paa.gov.pl/download/105/14759/Poland-JCreport2015.pdf>

¹⁹² <http://www.rosatom.ru/en/press-centre/news/jsc-tvel-and-the-national-center-for-nuclear-research-of-poland-concluded-a-nuclear-target-supply-co/>

¹⁹³ THE CZECH REPUBLIC NATIONAL REPORT under the Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management Praha 2017.

Storage Facility (27 FA), while HEU (112 FA) has been sent to Russia for reprocessing. A Geological Repository is under study (site selection phase).

France – OSIRIS

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
/	Yes (France)	CEA CASCAD Cadarache	Cigéo Project Design Phase

OSIRIS Spent Fuel has been progressively sent at AREVA's La Hague facility in prevision for future potential retreatment. CEA also dispose of the CASCAD facility (commissioned in 1990), an Interim storage installation for various RR Spent Fuel. A Final Disposal solution is in the Design Phase in France, with these radioactive wastes expected to be accepted by the Cigéo Geological Repository.

Romania – Triga 2 Pitesti

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
~0 m3	No	Pool	/

The converted 14 MW TRIGA-reactor in Pitesti, Romania became fully operational in 2003. A contract to supply fresh LEU fuel was signed in November 2003. The final batch of LEU fuel was delivered to Pitesti in March 2006. The fuel was loaded into the reactor by May 2006, completing the full-core conversion. The last irradiated HEU fuel elements were removed from the TRIGA by May 2006 and following several years of cooling, the U.S.-origin HEU was shipped to the United States in 2008. IAEA assisted Romania and the NNSA in repatriating the remaining HEU, of Russian origin, in 2009. The final shipment of spent HEU fuel was transferred by air. Future operation of the reactor with LEU will generate 0.35 tons of U Metal. LEU spent fuel is held in on-site cooling ponds for a period of around 20-30 years, and Romanian policy is that this fuel is also to be repatriated to the country of origin under agreement at some point in the future¹⁹⁴.

The Netherlands – HFR

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
6.2 m3 (in COVRA all RR Spent Fuel) ¹⁹⁵	No	COVRA (Long-Term)	For 2130

Spent fuel from research reactors is stored in the spent-fuel pools, prior to being shipped to COVRA (*The facilities of the Central Organisation for Radioactive Waste*) for long-term storage, without reprocessing. Periodic transports are arranged to ensure that the HFR pool always has sufficient storage capacity available to accommodate all elements present in the reactor core.

¹⁹⁴ Report on the National Programme Notification to the European Commission in relation to Directive 2011/70/EURATOM on the responsible and safe management of spent fuel and radioactive waste. August 2015.

¹⁹⁵ Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management October 2017 - The Hague, October 2017 - National Report of the Kingdom of the Netherlands for the Sixth Review Meeting

As of May 2006, the HFR has only used low enriched uranium (LEU) and the last HEU fuel elements from the HFR were shipped to COVRA in March 2011. A geological disposal facility is being considered around the 2130 timeline, owing to capital growth mechanisms in place to finance such an installation.

Portugal – RPI

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
No spent fuel	/	/	/

The RPI was converted from Highly Enriched Uranium (HEU) to Low Enriched Uranium (LEU) in 2007 and all HEU fuel was returned to the USA in 2008. The present LEU fuel will also be returned to the USA by May 2019.

Austria – TRIGA II Vienna

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
No spent fuel	/	in Pool before US repatriation	/

In October/November 2012 irradiated fuel elements from the research reactor were shipped to the Idaho National Lab and replaced by 77 19.8% enriched standard TRIGA fuel elements. With this new core the TRIGA reactor Vienna went critical on 27 November 2012. These fuel elements will be returned to the USA after 2025, if the parties of the contract (the Vienna University of Technology, the US- Department of Energy and EURATOM- ESA) don't agree upon an extension of the reactor operation.

Presently, the total number of fuel elements in the core is 76 (plus 9 fuel elements in the in-pool storage racks plus 5 fresh fuel elements in the fuel storage). The Institute of Atomic and Subatomic Physics has a total spent fuel storage capacity of 168 fuel elements.

Greece – GRR-1

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
<i>No estimate available</i>	/	Fuel Storage Pool before repatriation	/

The irradiated fuel from the past operation of GRR-1 is stored in the fuel storage pool inside the reactor building. The pool is an underground stainless-steel, 1.6m x 2.6m and 4m deep tank, offering 57 storage positions arranged in five groups.

All spent fuel from GRR-1 is to be transferred to the USA¹⁹⁶, according to an agreement with the US Department of Energy for shipment until 2019. Fuel purchases are required to be based on similar arrangements with foreign nuclear companies/organizations that will guarantee the return of spent fuel to the country of origin for storage or reprocessing.

¹⁹⁶ JOINT CONVENTION ON THE SAFETY OF SPENT FUEL MANAGEMENT AND ON THE SAFETY OF RADIOACTIVE WASTE MANAGEMENT – October 2017, NATIONAL REPORT OF GREECE

Denmark – DR-1, DR-2, DR-3

RR Spent Fuel Volume	Reprocessing	Interim Storage	Final Disposal
4.9 kg U (LEU), 15.8 l 30 GBq fission products 0,4 GBq actinides	/	In DR 3 building complex	/

Spent fuel from the research reactors DR 2 and DR 3 has been transferred to the USA according to an agreement with the US Department of Energy. The spent fuel from the research reactor DR 1 and about 233 kg of experimentally produced and irradiated spent fuel of power reactor type remaining from post-irradiation investigations in the former Hot Cell Facility are stored under safe and secure conditions awaiting a decision on the final management¹⁹⁷.

Denmark has since the Fifth Review Meeting continued the search for an international solution regarding the spent fuel from the research reactor DR 1 and 233 kg of experimentally produced and irradiated spent fuel. Until now this effort has proven unsuccessful. If an international solution cannot be found, the spent fuel will be included in the long-term management solution for radioactive waste in Denmark. Therefore, in the planning for a potential intermediate storage solution as well as a final repository, the spent fuel from the research reactor DR 1 and the 233 kg of experimentally produced and irradiated spent fuel is considered part of the radioactive waste to be stored or disposed of.

The Research Reactor Spent Fuel Management strategies appear closely similar among Member States – in most cases the spent fuel is to be returned to the supplier (France, US, UK or Russia), while others opt for disposal as high level waste. A few Member States expect return of the secondary waste from the reprocessing (e.g. Czech Rep) for interim storage prior disposal.

As of to date, only 15 Member States (i.e. with nuclear programmes) plan the construction, in 50 to 100 year time, of a deep geological repository for radioactive waste not acceptable in near surface disposal facilities. Some Member States with no nuclear programmes rely on shared disposal solutions, altogether half of the EU Member States considering this disposal option.

For most of the Member States with only limited nuclear installations (i.e. except France, Germany, the UK, for instance), the volume of radioactive wastes resulting from such installations does not economically justify the immediate construction of a geological repository. Thus, the hypothesis of joint installations for “small” High Level radioactive wastes producers (Netherlands, Poland, etc.) could seem a solution for these countries. This approach is currently being examined by a European multinational working group formed to study the feasibility of setting up a Development Organisation (ERDO) that would implement one or more shared geological repositories in Europe, with support from the European Commission¹⁹⁸.

¹⁹⁷ Joint convention on the safety of spent fuel management and on the safety of radioactive waste management – National Report

¹⁹⁸ http://www.erdo-wg.com/erdo_news.html#15_05_2017. See also related Research Programmes in the Research chapter of the present document

8.3. Mo-99 supply chain radioactive wastes

Even if its volume remains small as compared to spent fuel and concerns only few European producers (e.g. Curium/Petten, IRE/Fleurus), the radioactive waste generated from fission-based Mo-99 production can present specific problems due to the target processing and the switch to LEU targets.

Indeed, target dissolution remains the most important step from the standpoint of radioactive-waste generation. After reactor irradiation, U-235 targets are loaded into a hot cell where, after separation from aluminium and other claddings, U-235 plate or foil is inserted into a dissolver to separate the Mo-99 from other fission products and base materials. Typical volumes of radioactive liquid wastes generated from HEU targets are given in the table below:

Table 1: Actual characteristics of liquid waste per hot cell after production of 3000 Ci ⁹⁹Mo

Liquid from	Volume (l)	Content (g/l)	Activity (Mq/l)
Cell 1 ILW	8,2	NaOH 240 Al 20 U 0,005	⁸⁹ Sr 740 ⁹⁰ Sr 630 ¹³⁷ Cs 6400
Cell 2 ILW	10,5	NaNO ₃ 102 NaOH 29,6	¹⁰³ Ru 500 ¹⁰⁶ Ru 46 ¹²⁵ Sb 4,6
Cell 3 LLW	7,3	Na ₂ SO ₄ 115 NaI 0,06 Na ₂ SO ₃ 121 NaOH 16 NaSCN 4	¹⁰³ Ru 5 ¹⁰⁶ Ru 0,46 ¹²⁵ Sb 0,046
Cell 4 and 5 LLW	4,7	NaOH 12 NaNO ₃ 17	¹⁰³ Ru 0,040 ¹⁰⁶ Ru 0,0037

Table 20: Typical radioactive liquid wastes due to the production of 3000 Mo-99 Ci¹⁹⁹

The Mo purification process generates only small volumes of radioactive liquid waste with a relatively low activity level and consists mainly of aqueous solutions with a low concentration of acidic or alkaline media.

Radioactive Solid waste is generated mainly from spent ion exchange resins and absorber columns. Other types of radioactive solid waste are filter material from off-gas cleaning, such as activated charcoal filters or absolute filters from the hot cell. Small amounts of radioactive solid waste arise from the replacement of parts in the entire Mo production plant, such as valves, pumps, tubes, etc. The characteristics of the main radioactive solid-waste stream are compiled in the table below and come from the same reference as the previous table:

¹⁹⁹ RADIOACTIVE WASTE TREATMENT FROM MO-99 PRODUCTION FACILITY IN THE NETHERLANDS Rozé.M. van Kleef, COVRA NV <http://www.wmsym.org/archives/2001/25/25-5.pdf>

Table 11A actual estimated characteristics of solid waste per hot cell after production of 3000 Ci ⁹⁹Mo

Solid Waste, type	Components	Activity some days after production (MBq/syntacscontainer)
Cell 1, ILW	filters sinter metals tissues pipes/tubes	²³⁴ U 0.93 ²³⁵ U 0.029 ²³⁶ U 0.0037 ²³⁹ Pu 0.011 ⁸⁹ Sr 140 000 ⁹⁰ Y 500 ⁹¹ Y 150 000 ⁹⁵ Zr 150 000 ⁹⁵ Nb 10 000 ⁹⁵ Zr 150 000 ¹⁰³ Ru 120 000 ¹⁰⁶ Ru 1 600 ¹⁴¹ Ce 290 000 ¹⁴⁴ Ce 31 000 ¹²⁵ Sb 17 To be transported in type A container after two months decay-time
	Absorber columns Ion exchangers PVC tubes stainless steel components tissues	¹³¹ I 23000 ¹⁰³ Ru 420000 ¹⁰⁶ Ru 23000
Cell 3, ILW	Absorber columns polyethylene bottles	¹⁰³ Ru 30000 ¹⁰⁶ Ru 3300
Cell 4, LLW	tissues	Mo-99 tracers
Cell 5, LLW	tissues	Mo-99 tracers
Replacement components when necessary, ILW/LLW	dissolvers drop collector in cell storage tanks	various activity

Table 21: Typical solid waste due to the production of 3000 Mo-99 Ci

The use of LEU targets is being promoted by the international community to avoid the proliferation issues linked with the use of HEU. However, the volume of uranium radioactive waste stemming from these targets is estimated to grow six-fold²⁰⁰. Concerning research reactor fuel, the transition from HEU to LEU is already almost complete within EU (last major player being BR-2 with a transition under study). LEU fuel assemblies currently generate higher quantities of long-life radioactive wastes (Pu, Actinides...).

The integration to Mo-99 supply chain of radioactive waste compacting installations, such as ANSTO's Synroc project²⁰¹, could optimize radioactive waste volume and storage of intermediate and high-level radioactive wastes coming from target reprocessing. ANSTO is currently designing and building the so-called Synroc radioactive waste treatment plant (*expected to be operational from late 2019*) as part of its MPF project.

²⁰⁰ Radioactive Waste Issues Related to Production of Fission-based Mo-99 by using Low Enriched Uranium (LEU) / Muhmoodul Hassan and Ho JinRyu - KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon, Republic of Korea.

²⁰¹ ANSTO has for about 40 years invested in research and development of a technology called Synroc (short for synthetic rock) to provide a matrix for immobilization and final disposal of various types of intermediate-level and high-level radioactive wastes, including long-lived actinide-rich waste streams. In the synroc process, the radioactive liquid waste is mixed with additives to create a slurry that is then dried to produce a free-flowing powder. The resultant powder is first thermally treated and then dispensed into cans and sealed. The cans are hot isostatically pressed, heated, and then pressure is applied. Under these conditions the powdered mixture is formed into a solid ceramic or glass ceramic block of well-defined composition. The canister is designed to collapse and form a cylindrical shape suitable for maximum waste storage efficiency.

Table 3. The radioactive waste generation from HEU and LEU targets for ⁹⁹Mo production [17]

	HEU targets	LEU targets
²³⁵ U enrichment, %	93	19.75
U-total, g	16.1	93.7
⁹⁹ Mo, Ci (mg)	532 (1.11)	545 (1.13)
total Mo, mg	9.8	10.0
²³⁹ Pu, mg	0.44	11.8
total α produced, μCi	62	793

Figure 40: Radioactive Waste generation differences. HEU vs LEU targets

Radioactive Waste strategy: Curium/Petten has agreements with NRG for radioactive waste management, hence the problem is solved the same way as for the HFR spent fuel (see above). As concerns IRE, information on the radioactive waste management strategy was not available for this study.

8.4. Sealed sources

More details on sealed sources can be found in Appendix A.1

8.4.1. High Activity Sealed Sources (HASS)

The EC recently issued a working paper²⁰² relative to HASS (High activity sealed sources). European Union Council Directive 2003/122/EURATOM (so-called 'HASS Directive') requires EU Member States to implement several measures to guarantee the safety and security of high-activity sealed radioactive sources and to search for orphan sources. This working paper discusses the results of the recent HASS Directive implementation review and the results of a supporting study draft under the EU CBRN Action Plan (Chemical, Biological, Radiological and Nuclear Security).

Inventory

According to the data reported by EU Member States, the European inventory of HASS comprises about 30 700 HASS²⁰³, of which 50% are accounted for by Germany and France alone (see below). Nine Member States have an inventory of less than 100 HASS. About 3 200 HASS holders are recorded in 24 Member States, of which 63% are to be found in Germany, France, Poland and the UK. Typically, there are 1 to 40 individual HASS per holder.

²⁰² COMMISSION STAFF WORKING DOCUMENT: Control of high-activity sealed radioactive sources in Europe: Implementation of Directive 2003/122/EURATOM in EU-27 and the current EU regulatory development activities SWD(2015) 84 final. Directive 2003/122/Euratom is now repealed, with effect from 6 February 2018, by Directive 2013/59/Euratom (the new Basic Safety Standards Directive), which incorporates the main provisions of the Directive and harmonises them with the IAEA guidance on radioactive sources.

²⁰³ Total number of sealed sources in Europe could not be found in the national reports. See next paragraph

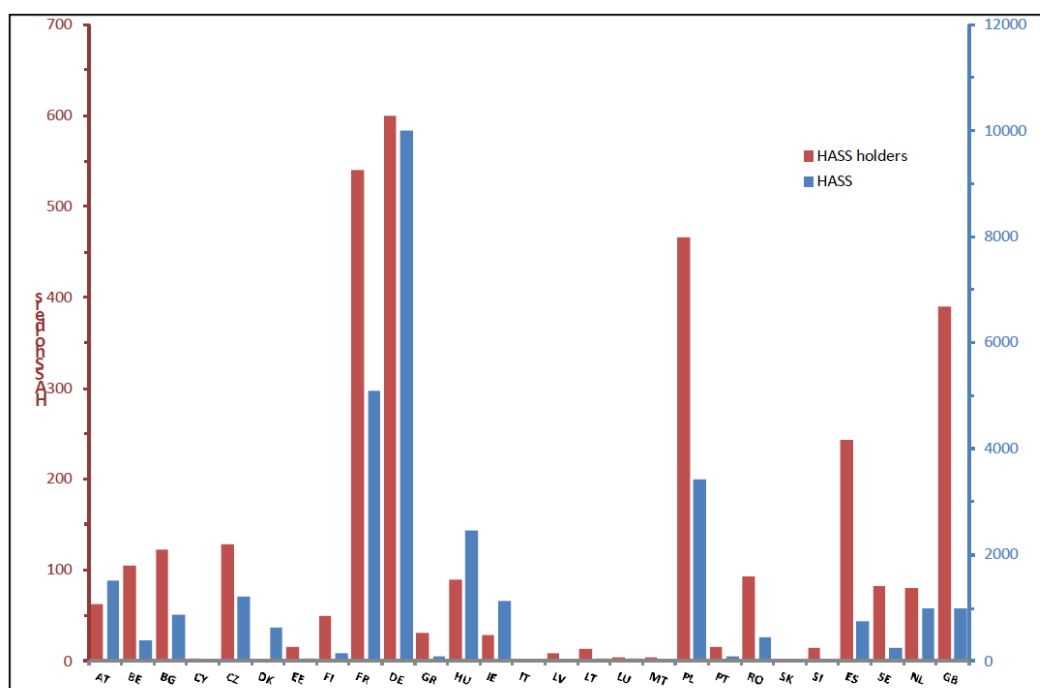


Figure 41 : Number of HASS holders (red) and High activity sealed sources (blue) in Europe

Implementation of the HASS Directive principles is going well in the EU, although there are significant differences in implementation practices among the EU Member States. The low number of HASS-related inquiries submitted to the Commission over the years indicates that the Directive requirements are well-understood and accepted.

The authorities in the EU Member States advise the following recommendations to keep radioactive sources under control and to manage incidents safely:

- systems for ensuring traceability of radioactive sources throughout their life cycle;
- regular inspections;
- physical-protection requirements in high-risk facilities;
- compulsory training of personnel;
- monitoring to detect radioactive materials in strategic locations;
- information exchanges among national and international competent authorities;
- public information;
- testing of pre-established plans to prevent and respond to incidents involving HASS.

EU Member States had until 6 February 2018 to transpose the new BSS Directive into their national legislation. The Commission encourages each Member State to consider the above recommendations when redrafting their national regulations and guidelines on safety and security of radioactive sources.

Comments raised by the Directive

The HASS Directive requires sources holders i) to return each disused source to the supplier or ii) place it in a recognised installation or iii) transfer it to another authorised holder without undue delay after it goes out of service, unless otherwise agreed by the competent authority.

This directive prompts several comments:

- As “undue delay” is not defined precisely in the Directive, the period prior to mandatory transfer greatly varies among Member States, ranging from less than one year to several years or no pre-defined period. A “good practice” would consist of defining a reasonable maximal period for removal of disused sources from users’ premises, e.g. maximum 2 years, in a regulation.
- Takeback provisions alone do not guarantee the effective removal of disused sources from holders’ premises. Besides, financial arrangements, such as monetary deposits by the holders or suppliers may be necessary. Such arrangements, financed by the source-user community, would also be available for the long-term management of disused HASS transferred to a recognised storage facility. However, the source manufacturers industry in the EU is composed of numerous small companies, that would not necessarily have the financial means to secure the long-term management of disused sources.
- In addition, the proper management of disused sources necessitates solid knowledge of the source design, composition and structure; for long-life sources, recycling/radioactive waste disposal may intervene 30-40 years after its fabrication date. Thus, know-how transfer has to be secured over time, which is not always possible for small companies.

Hence, although the HASS directive and the BSS, which replaces it, call for a possible return of disused sources to the supplier, this option may pose hard-to-resolve practical problems.

8.4.2. Sealed sources disposal

The challenges concerning the safe management of disused sources are multiple:

- Disused sources are returned to manufacturers, years after their fabrication. Manufacturers often gather large volumes of disused sources, without necessarily having the sufficient technical, financial and human resources to handle source characterization, conditioning and packaging for long-term storage/disposal²⁰⁴;
- Detailed information concerning source structure/components is required for source dismantling operations and disposing of a detailed database enables the appropriate handling of such operations, often several decades after source manufacturing. Initiatives such as the International Catalogue of Sealed Radioactive Sources and Devices (ICSRS) published by the IAEA should be supported by the European Commission, to have ensure a technical database is available to assist in disused source dismantling;
- Disposal installations for Long lived Intermediate and high-level radioactive waste are not available²⁰⁵ in the vast majority of EU-28 countries. In the interim, close relations between manufacturers and national radioactive wastes agencies for

²⁰⁴ ANDRA Presentation – SAMIRA conference 20-21 Mars 2018,

“Waste management solutions are often perceived as a low valued process, far from the heart of their activity, heavy, long, restrictive and expensive. To address this ANDRA has put in place a more developed service and advice level than for electronic producers.”

²⁰⁵ Commission Staff working document – progress of implementation of council directive 2011/70/EURATOM SWD (2017) 159.

grouping/sorting and dismantling activities of disused sources should be encouraged to prepare the long-term management of such sources (see this chapter's conclusion).

Reliable inventories are needed

Adequate actions necessitate precise knowledge of the inventories. The EU-28 wide quantitative data covering the use of sources like those gathered every year in Japan and sorted by users, by radioisotopes, etc., are generally not available. The analysis of the Bulgarian and French examples is nevertheless interesting.

In Bulgaria, the Institute for Nuclear Research and Nuclear Energy (INRNE) operates the Novi Han Repository (NHR), which is currently used as a central storage facility for institutional radioactive wastes. A detailed inventory of the sources stored in the facility²⁰⁶ led to the following estimate: roughly 315 000 units are stored inside the facility. Almost 250 000 sources (~80%) are from smoke detectors (152000 Pu-238 and 94000 Am-241).

Type	Amount
Long-lived (Am-241)	94101
Long-lived (Pu-239)	152806
Very short lived	827
Short Lived (various)	27489
Short Lived (Co-60)	4327
Short Lived (Sr-90)	10066
Short Lived (Cs-137)	7882
Long-lived (Ra-226)	3056
Long-lived (Various)	12049
Neutron Sources	231
Unknown	1350

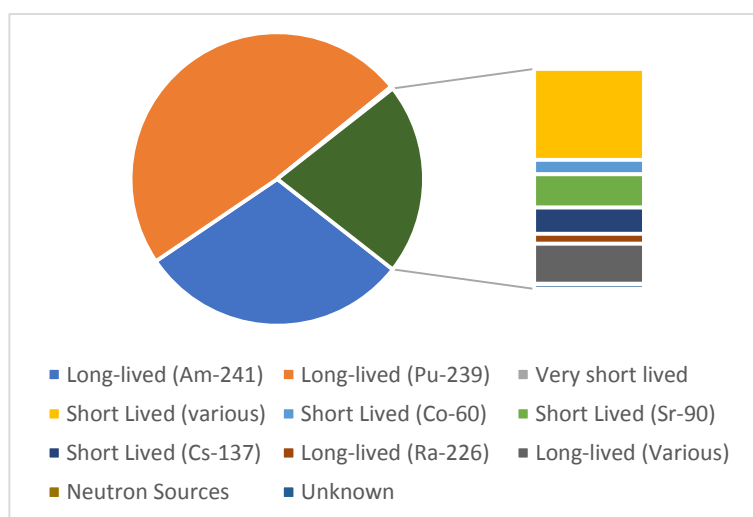


Figure 42: Bulgarian radioactive sources inventory

Currently, disused sources are stored without any preliminary dismantling from the main device, shielding or package. Conditioning and radioactive waste packaging operations are being studied. Until a final repository is available, the only solution lies in an interim storage facility for conditioned radioactive wastes and disused sealed sources.

In France, the situation is similar. The inventory of disused sealed sources encompasses roughly 2 300 000 disused sealed sources²⁰⁷ (largest part coming from smoke detectors), including 5 000 HASS (less than 0.1%), with the following breakdown²⁰⁸ in terms of radioactive waste types:

²⁰⁶ Current Approaches on the Management of Disused Sealed Sources in Bulgaria.

http://www.iaea.org/inis/collection/NCLCollectionStore/_Public/37/038/37038490.pdf

²⁰⁷ https://inventaire.andra.fr/sites/default/files/publishpaper/2015_catalogue_familles/files/docs/all.pdf

²⁰⁸ NEA Workshop on the Management of Non-Nuclear Radioactive Waste – May 2017 – ANDRA - National Circumstances and Approaches: France

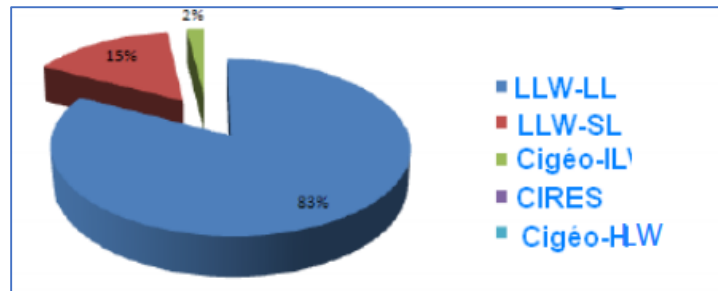


Figure 43: Disposal of Radioactive Sources in France

Roughly 98% of sealed sources could be disposed of in surface or sub-surface facilities (83% of LLW Long-lived sealed sources and 15% of LLW short-lived sealed sources), the remainder is expected to be disposed of in Cigéo, the French geological repository. France does not currently have a disposal facility for low and intermediate-level long lived radioactive waste (Half-life > 31 years); the ANDRA is currently conducting grouping and conditioning activities. At the end of 2016, 822 m³ of I&LLW LL radioactive wastes coming from non-power applications (including sealed sources) were stored in a dedicated storage facility.

Regroupment



Collecting and packages providing

Disposal



Sorting / Treatment



Storage (for low and intermediate level waste, long lived)



Figure 44: ANDRA approach for non-electronuclear activities (courtesy from ANDRA)

8.5. Other radioactive waste from non-power applications

8.5.1. Unsealed Sources, X-Ray Generators and Accelerators

Unsealed sources generally have low activity and a short half-life and are managed through natural decay (e.g. unsealed sources for therapy and for Industrial Leakage Detection). There are no major a priori concerns regarding the 'other' category aside from standard safety and radioprotection issues.

This is also the case for X-Ray and small accelerator machines, which essentially pose radioprotection issues.

Large installations such as the CERN generate more radioactive waste that exists in diverse forms: electro-magnets, electrical wires, metallic, technological waste, activated concrete, etc. The CERN waste treatment strategy includes:

- Storage of radioactive waste in a building that formerly hosted an accelerator (currently, some 7000 m³ of waste are stored)²⁰⁹;
- As far as possible, free release of short-lived LLW under the Swiss clearance process.

8.5.2. Radioisotopes-producing cyclotrons

Although cyclotrons are not associated with high-level radioactive waste management, it is interesting to investigate whether they elicit radioactive waste-related questions or not, as they may become alternatives to research reactors for radioisotopes production.

Operating a cyclotron is relatively safe per se and does not generate large amounts of radioactive waste. As only short half-life radionuclides are produced, radioactive wastes generated during operations also have a short half-life. Safety is ensured by thick concrete-wall shielding around the cyclotron room (vault) to prevent any radiation leak.

However, the accelerated particles in the cyclotron, and the indirect particle production in the targets (mainly neutrons) are the cause of an indirect activation of the cyclotron, the structure and equipment present in the vault (material, air and concrete activations). Even if these contaminations are limited to a residual low-activation risk, they can induce non-negligible decommissioning/dismantling and radioactive waste management costs.

The example of concrete activation levels for two cyclotron dismantling projects is given below:

Isotope	Measured activity (Bq/g)	UCL (Bq/g)
Co-60	0.068	0.1
Cs-134	0.005	0.1
Eu-152	0.083	0.1
Eu-154	0.010	0.1
Mn-54 *	0.016	0.1
Total	0.18	0.1

Figure 45: Decommissioning of 20-year-old 17 MeV Scanditronix cyclotron (~40 µA)

Note: UCL: unconditional clearance level at which material can be released as non-radioactive – Source²¹⁰

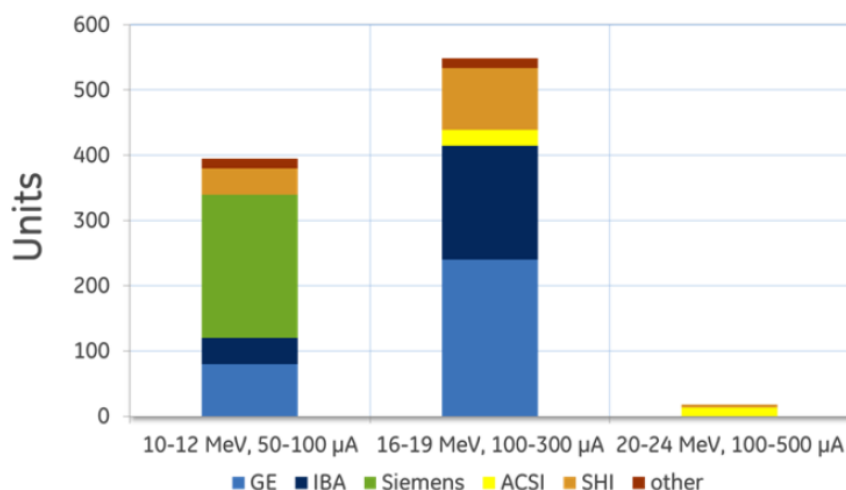
²⁰⁹ Samira Conference. 21 March 2018. ANDRA presentation

Table 1. Type of transport package and major properties			
Radioisotope*	Bin(Stopper, Targetry)	Body(Magnet, Cover)	Shielding Housing
	²² Na, ⁵⁴ Mn, ⁵⁶ Co ⁵⁸ Co, ⁶⁰ Co, ⁶⁵ Zn	⁵⁴ Mn, ²² Na, ⁵⁶ Co, ⁴⁰ K, ⁶⁰ Co, ⁶⁵ Zn	⁵⁴ Mn, ⁴⁰ K, ⁶⁰ Co
Maximum estimated radioactivity (MBq)	61.61	500	92.3
Surface dose rate (mSv/h)	0.5	0.0005	0.005
Weights (kg)	11.2	20,000	9,230

Figure 46: Radioactive waste collected during cyclotron dismantling (SNUH Facility)

This activation generates low-level radioactive waste: for the 17 MeV Scanditronix cyclotron dismantling, 40 tons of LLW were collected, and in the case of the SNUH cyclotron, 30 tons of LLW were generated. Decommissioning/Dismantling of cyclotrons has to be taken into account from the design phase onwards, as many solutions exists to reduce the final activation following definitive shutdown (e.g. *vault geometry, reinforced shielding, wall coatings*).

No precise figure can be found on the EU cyclotrons installed base, a worldwide estimate in 2014 (based on cyclotrons manufacturers data) numbered 1000 cyclotrons. Estimates evaluate to roughly 200 the number of cyclotrons used for medical purpose within EU²¹¹. Cyclotrons can be operated during 20 to 40 years, depending on size and type of use.



Estimated global cyclotron numbers by various manufacturers
(with data from ACSI, GE, IBA and Siemens, Sumitomo data estimated)

Figure 47: Estimated global cyclotron numbers by various manufacturers

Cyclotron decommissioning costs can vary from several hundreds of thousands²¹² to a few million euros, depending on the size of the installation and the cyclotron characteristics. These costs are non-negligible when compared to the investment cost. Investment decisions must take them into account.

²¹⁰ Sunderland J. et al. "Considerations, measurements and logistics associated with low energy cyclotron decommissioning (2011)", AIP Conf. Proc. 1509, 16 (2012): <http://dx.doi.org/10.1063/1.4773931>

²¹¹ <http://www.cyclotron-nantes.fr/spip.php?article8> consulted on 5/7/2018

²¹² <http://www.j.sinap.ac.cn/nst/EN/article/downloadArticleFile.do?attachType=PDF&id=506>

8.5.3. Tritiated radioactive waste from non-power applications

Nuclear power plants and nuclear fuel reprocessing facilities are responsible for the overwhelming part of Tritium generation and effluents²¹³. Some non-power applications can nevertheless be mentioned as Tritium effluent sources:

- The production and use of marked molecules for medical or research applications. In the Amersham installation (UK), ~100 TBq are generated per year. The same orders of magnitude are registered for similar laboratories in Saclay (France).
- The manufacturing of radio-luminescent equipment containing gaseous tritium. An "Exit" panel may contain 0.1, to 0.5 TBq of Tritium.
- The Uranium target dissolution after irradiation in research reactors for Mo-99 production. Tritium is generated during the irradiation phase (1.6 GBq per target²¹⁴). Assuming that 80 targets are needed each week to satisfy global demand for Mo-99, 6.5 TBq are generated each year.

Tritium is a very low energy β -emitting radioisotope, with a 12.3 years half-life. The global Tritium issue (including the tritium stemming from nuclear energy) was the subject of a comprehensive White Paper, published by the French ASN in 2010 and recently updated²¹⁵. The conclusions of this study were:

- Due to its low radiotoxicity, the global impact of the tritium releases in France remains low, in the few micro-Sievert range.
- The main form of tritium in the biosphere is tritiated water, and the main exposure mode is ingestion.
- Tritium management currently remains difficult and the White Paper evidences the necessity of conducting complementary studies to consolidate the data and knowledge about tritium's behaviour in the environment.

8.5.4. Radioactive waste challenges: conclusion

Radioactive waste produced by non-energy applications remains a very low fraction of the radioactive waste generated by nuclear energy. The radioactive waste strategy is similar in all EU MS, and consists in:

- storing the radioactive waste, according to its nature and activity;
- in some countries, releasing the waste according to a strict clearance process;
- waiting for natural decay or the availability of a final disposal solution for the non-released radioactive waste.

It is recommended that the EC verifies, at the pan-EU level, that non-energy radioactive waste is adequately inventoried, packaged and collected, sorted, cleared or buried (VLLW), or stored (higher level or long-lived radioactive waste) in a dedicated installation, under close surveillance by an independent national body.

²¹³ Annual global atmospheric releases from all nuclear power plants are in the range of 6000 TBq, while liquid released represent 10 000 to 12 000 TBq per year. For global Nuclear fuel reprocessing facilities, values are approaching 10 000 TBq per year and 300 Tbq per year for Liquid and Atmospheric releases respectively.
<https://www.asn.fr/sites/tritium/>

²¹⁴ https://www-pub.iaea.org/MTCD/Publications/PDF/te_1051_prn.pdf

²¹⁵ Livre Blanc du Tritium (Tritium White Paper). ASN. <https://www.asn.fr/sites/tritium/>. See also <http://www.irsn.fr/FR/Larecherche/publications-documentation/fiches-radionucleides/environnement/Pages/tritium-environnement.aspx#.WxTDuO6FOUk> (in French)

9. Safety challenges

9.1. Overview of EU research reactors

Please note: Based on the IAEA Research Reactor Database, the installations that do not declare producing Radioisotopes have not been retained in the analysis.

(<https://nucleus.iaea.org/RRDB/RR/ReactorSearch.aspx>)

As of April 2018, 209 Research Reactors have been identified in the EU-28, with the following status:

- 37 are in operations (13 of which are used for RI Production);
- 3 are planned, including 1 already under construction;
- 16 are in a state of permanent/extended/temporary shutdown;
- 28 are being decommissioned;
- 125 have been decommissioned.

Most often, RI production per research reactor is not publicly disclosed.

Countries	Reactor Name	Type	Power	First criticality	Status
Austria	TRIGA II VIENNA	TRIGA MARK II	0,25 MW _{th}	1962	In Operation
Belgium	MYRRHA	FAST	85 MW _{th}	/	Planned
	BR-1	GRAPHITE	4 MW _{th}	1956	In Operation
	BR-2	TANK IN POOL	100 MW _{th}	1961	In Operation
Bulgaria	No research reactor used for Radioisotopes production				
Croatia	No research reactor used for Radioisotopes production				
Cyprus	No research reactor used for Radioisotopes production				
Czech Republic	LVR-15 REZ	TANK WWR	10 MW _{th}	1957	In Operation
Denmark	No research reactor used for Radioisotopes production				
Estonia	No research reactor used for Radioisotopes production				
Finland	No research reactor used for Radioisotopes production				
France	REACTOR JULES HOR	TANK IN POOL	100 MW _{th}	/	Under Construction
	ILL	HEAVY WATER	58,3 MW _{th}	1971	In Operation
	ORPHEE	POOL	14 MW _{th}	1980	In Operation
Germany	FRMZ	TRIGA MARK II	0,1 MW _{th}	1965	In Operation
	FRM II	POOL	20 MW _{th}	2004	In Operation
Greece	No research reactor used for Radioisotopes production				
Hungary	BUDAPEST RES. REAC	TANK WWR	10 MW _{th}	1959	In Operation
Ireland	No research reactor used for Radioisotopes production				
Italy	TRIGA RC-1	TRIGA MARK II	1 MW _{th}	1960	In Operation
Latvia	No research reactor used for Radioisotopes production				
Lithuania	No research reactor used for Radioisotopes production				
Luxembourg	No research reactor used for Radioisotopes production				
Malta	No research reactor used for Radioisotopes production				
Netherlands	PALLAS	to be defined	?	/	Planned
	HOR	POOL	2 MW _{th}	1963	In Operation
	HFR	TANK IN POOL	45 MW _{th}	1961	In Operation
Poland	MARIA	POOL	30 MW _{th}	1974	In Operation
Romania	TRIGA II PITESTI - SS	TRIGA DUAL CORE	14 MW _{th}	1980	In Operation
Slovakia	No research reactor used for Radioisotopes production				
Slovenia	TRIGA- MARK II LJUB	TRIGA MARK II	0,25 MW _{th}	1966	In Operation
Spain	No research reactor used for Radioisotopes production				
Sweden	No research reactor used for Radioisotopes production				
United Kingdom	No research reactor used for Radioisotopes production				

Table 22 : European research reactors

The EU Member States Research Reactors typology vary widely in terms of technology (e.g. *Pool, Tank in Pool, Triga, Graphite*), power (*few kW to dozens of MW*) and age (*most being over 40 years old*).

9.2. Research reactor safety regime

At the European Level, the Safety Regime for Research Reactors has been defined through “Council Directive 2009/71/Euratom of 25 June 2009 establishing a Community framework for the nuclear safety of nuclear installations”. This regulation and its amendments (Council Directive 2014/87/EURATOM of 8 July 2014 amending Directive 2009/71/Euratom establishing a Community framework for the nuclear safety of nuclear installations) apply to Research Reactors.

In particular, two provisions of Directive 2014/87 specifically concern research reactors:

*(20) Following the nuclear accidents at Three Mile Island and Chernobyl, the Fukushima nuclear accident once again highlighted the critical importance of the containment function, which is the last barrier to protect human beings and the environment from radioactive releases resulting from an accident. Therefore, the applicant for a licence to build a **new** power or **research reactor** should demonstrate that the design limits the effects of reactor core damage to within the containment vault, i.e. the applicant should prove that a large or unauthorised radioactive release outside the containment is extremely unlikely, and such an applicant should be able to demonstrate with a high degree of confidence that such a release will not occur.*

*(25) In line with a **graded approach**²¹⁶, the implementation of the provisions of this Directive depends on the types of nuclear installations on the territory of a Member State. Therefore, when implementing these provisions in national law, Member States should consider the potential magnitude and nature of the risks posed by the nuclear installations that they plan or operate. In particular, the graded approach should concern those Member States that keep only a small inventory of nuclear and radioactive materials, e.g. those linked to the **operation of smaller research reactor facilities**, which in the event of a severe accident would not engender consequences comparable to those generated by nuclear power plants.*

Directive 2014/87 provides also for periodic topical peer reviews.

At a national level, European regulations are applied as a baseline framework, and are supplemented by national regulations and recommendations that may differ from one country to another, especially for Research reactors.

Member States regularly report on the implementation of the Euratom Directives. The latest release was published during the 7th Review meeting of the Contracting Parties to the Convention on Nuclear Safety (CNS) Vienna, 27 March-7 April 2017²¹⁷.

²¹⁶ Bolded characters are from the authors of this study.

²¹⁷ https://ec.europa.eu/energy/sites/ener/files/documents/implementation_report_rm_2017.pdf

9.3. IAEA Safety issues of research reactors

The Incident Reporting System for Research Reactors (IRSRR) is operated under the IAEA programme on the Safety of Research Reactors and aims to collect, analyse and disseminate information on a worldwide scale about unusual events that have occurred at research reactors. Safety issues and trends are identified, and programme and activities are updated accordingly.

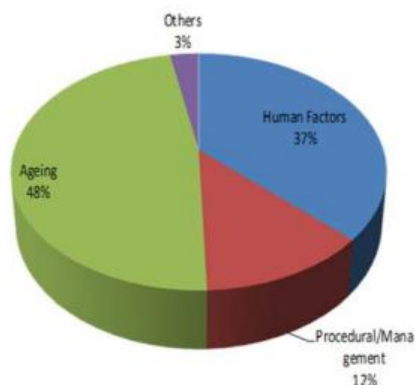


Figure 48: Statistics on the Root Causes of the events reported to the IRSRR – August 2016

The analysis of the events collected by IAEA²¹⁸ shows the predominance of Ageing-induced incidents — 48% of reported events (*main causes being improper design including material selection; inadequate actions to minimize ageing degradation; poor water-chemistry programme; inadequate initiatives for detecting ageing degradation such as periodic tests, inspections or observations during walkthroughs; weakness in safety culture*) and Human Factor induced incidents — 37% of reported events (*main causes being the lack of adequate training; deficiency in the operating procedures; inadequate consideration of human factors in operating procedures, including maintenance planning*).

For the IAEA²¹⁹, the analysis of the root causes of the events reported in the IRSRR leads to the following recommendations:

- i. Establishing a systematic ageing management programme, including taking ageing into account in the design and fabrication stages, and during operation of the reactor and experimental facilities;
- ii. Enhancing the safety culture (*management responsibility, effective communication at all levels, proper planning and preparation of work, effective use of approved operating procedures, improving housekeeping*);
- iii. Establishing an effective Management System/QA programme for different phases in the research reactor's lifetime (*including clear definitions of functions and responsibilities, management review and assessment, communicating operating experience feedback*);
- iv. Improving operating procedures (*Development process: Involvement of operational personnel; Consideration of human factors; Adequate review and approval process; Adoption of a trial period of use before formal approval; Training on the use of procedures; Periodic review and updating to incorporate acquired experience*);
- v. Establishing systematic training and retraining programmes (*particular emphases should be placed in on-the-job training*);
- vi. Considering human factors at different stages in the research reactor's lifetime;
- vii. Improving administrative aspects of maintenance, periodic testing, and inspection activities (*use of approved procedures, training of maintenance personnel, administrative oversight of maintenance- implementation of work authorizations-, conducting analyses of maintenance records for failure prediction and continuous improvement*).

²¹⁸ Safety Issues and Trends and IAEA activities on Research Reactor Safety - A. M. Shokr - Research Reactor Safety Section/Division of Nuclear Installation Safety - August 2016

²¹⁹ Safety of Research Reactors Training Material - IAEA-TCS-64/CD - M-5.1 - Incident Reporting System for Research Reactors (IRSRR)

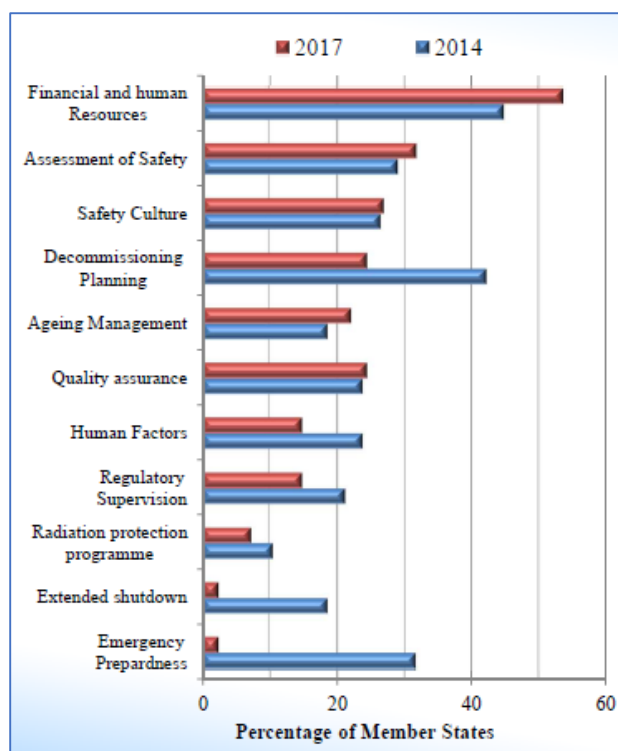


Figure 49: IAEA survey on RR safety issues among IAEA member states

During the 2017 International Meeting on the code of conduct's impact on the Safety of Research Reactors, IAEA member states were surveyed via self-assessments about the different safety issues that should be improved in the near future as concerns Research Reactors; results are given in the Figure 46.

In addition to previously identified issues (*ageing management, safety culture, human factors, etc.*) they identified "Financial and human resources", and "Decommissioning Planning" as the most critical safety issues in the immediate future.

These self-assessments and associated discussions showed that ageing of both facilities and staff, as well as lack of adequate decommissioning planning remain the major issues. However, the

discussions also showed that (based on the lessons learned from the Fukushima accident) consideration of interaction between human, technical and organizational factors need further attention. In several countries, the discussions also showed the need to establish effective integrated management systems that support establishment and maintenance of a safety culture.

In order to provide greater detail about the typical safety issues affecting European Research Reactors, the conclusions of the IAEA INSARR missions are being closely analysed.

9.4. INSARR mission analysis

The objective of the INSARR mission is to conduct safety evaluations of research reactors according to the IAEA safety standards and to provide recommendations and suggestions for reactor-safety improvements. The review covers all the safety aspects of reactor operations, including:

- a. Regulatory supervision;
- b. Operational organization and reactor management
- c. Safety committee;
- d. Training and qualification of operating personnel;
- e. Safety Analysis Report (SAR);
- f. Safety analysis;
- g. Operational Limits and Conditions (OLCs),
- h. Conduct of operations;
- i. Maintenance, periodic testing and inspection;
- j. Utilization and modifications;
- k. Operational radiation protection and waste-management programme;
- l. Emergency planning;
- m. Quality-assurance programme;
- n. Decommissioning plan.

INSARR Missions have been conducted on a global scale by the IAEA over a 20-year period. The following table details the INSARR missions conducted in the European Union.

Year	Country	Entity
1999	Belgium	BR2
1987	Finland	VTT
1987	Norway	IFE
1988	Norway	HBWR
1989	Hungary	KFKI
1990	Bulgaria	IRT-Sofia
1992	Portugal	LNETI
1992	Romania	Pitesti
1993	Greece	GRR-1
1993	Hungary	KFKI
1999	Finland	FiR-1
2000	Netherlands	HOR
2000	Poland	Maria
2001	Greece	GRR-1
2002	Netherlands	HFR
2002	Romania	Pitesti
2003	Czech Republic	LVR-15
2005	Netherlands	HFR
2007	Norway	Halden RR
2011	Netherlands	HFR
2011	Romania	INR
2012	Slovenia	IJS
2013	Italy	LENA
2014	Poland	NCBJ
2016	Portugal	RPI
2016	Netherlands	HFR
2017	Norway	JEEP II Research Reactor

* Main EU-28 RI producers are highlighted in Blue

Table 23: INSARR missions - European Research Reactors

The recommendations of two²²⁰ INSARR missions, for which the Final Report has been publicly released, are summarized in the next table. Some findings are similar for the two INSARR missions and illustrate the key Safety Issues confronting Research Reactors (Pool tightness, update of the OLC²²¹, external hazards evaluation, safety analysis update, etc.).

²²⁰ Report of the INSARR Mission to the High Flux Reactor (HFR), Petten, The Netherlands 4 - 11 October 2016.
Report of the INSARR Mission to the Slovenia TRIGA MARK- II Research Reactor Ljubljana, Slovenia 12-16 November 2012.

²²¹ Operating Limiting Conditions.

Table 24 : INSARR findings on 2 examples

	INSARR Mission / Triga Mark-II Slovenia – Nov. 2012	INSARR Mission / HFR Netherlands – Oct. 2016
Operating organization & Human Resources	- The roles and responsibilities for safety of the Head of the Reactor Infrastructure Centre, reactor manager and reactor operating staff should be defined by the IJS in a formal document. - The duties and responsibilities of the Technical Manager (reactor manager) for reactor operations should be covered by a full-time position in the IJS organization and the necessary funds should be ensured by the Government for this purpose.	- Revising the reactor operating organizational structure to avoid overlap and potential conflicts between different managers; - Considering establishing administrative procedures and practical arrangements to ensure the RP independence. - Filling in the position of Maintenance Manager, - Evaluating, with respect to safety, the situation of having the same person carrying out the functions of Reactor Manager for the HFR and Low Flux Reactor
Training and qualifications	/	- It is recommended that a requirement be established on requalification of certified operating personnel should they be away, for any extended period of time, from the activities that they are licensed for. - Training on the application of the management system should be conducted for HFR staff.
Safety committee(s)	The Terms of Reference of the Safety Committee (SC) should be revised to include the advisory role of the Committee to the IJS director and to ensure consistency with the IAEA Safety Standards and international good practices concerning the items to be reviewed by the committee.	For enhancing the effectiveness of the reactor safety committee, it is recommended that the committee be informed by NRG management about the implementation of the actions associated with its recommendations.
Decommissioning plan;	It is suggested to use the records of different environmental radiation measurements to establish baseline data for the ultimate decommissioning of the reactor facility. In the event of gaps in these data, actions must be taken to complete them.	Effective coordination and cooperation between JRC and NRG should be ensured in drafting the revised version (and subsequent revisions) of the HFR decommissioning plan. Arrangements should be defined and established to ensure the availability of HFR's most knowledgeable personnel and up-to-date documentation required for safe decommissioning.
Safety culture;		Concerted efforts have been made by NRG to promote and further develop a strong safety culture. To supplement these efforts, the NRG senior management should ensure that self-assessments and independent assessments of leadership for safety and safety culture are conducted on regular basis.
Safety analysis;	- The technical content of the revised SAR should be in accordance with the IAEA Safety Standards. SAR should include a revised version of safety analysis that should cover selection of Postulated Initiating Events (PIEs), description of event sequence and comparison against acceptance criteria. - The operating procedures should be completed (revised) to cover all the operations of significance to safety and to ensure realization of the OLCs, including the procedures for fuel loading into the reactor core.	- It is recommended that measures aimed at minimizing accidental water leakage through the sub-pile room and the pipes penetrating the reactor pool be defined and implemented. This is to reduce the risk of core un-coverage, taking into consideration an earthquake and loss of the electrical power supply combination. - Engineering measures should be implemented to protect the pool floor from the possible damaging effects of accidental conditions that may occur during handling of heavy loads, such as transfer casks.

	INSARR Mission / Triga Mark-II Slovenia – Nov. 2012	INSARR Mission / HFR Netherlands – Oct. 2016
Site evaluation and protection	- The fire hazard analysis should be completed as soon as possible and, accordingly, fire detectors (or automatic extinguishers as necessary) should be installed in all reactor areas having potential fire hazard. To reduce the fire load, all non-used inflammable materials should be removed from the reactor building. - The emergency ventilation system should be equipped with charcoal filters. Periodic testing of the efficiency of the filtration system should be performed.	- Seismic safety analysis of HFR was conducted using a conservative ground response spectrum. To confirm that sufficient safety margins exist, piping and other service lines important to safety should be checked for adequate seismic capacity. - The corrective actions resulting from the facility seismic walk-down and subsequent evaluation should be implemented in a timely manner. A programme for monitoring site characteristics during the operations phase, in accordance with IAEA safety standards No NS-R-3, should be developed and implemented. This should be oriented to evaluate possible impacts on the safe operations of the reactor
Operational limits and conditions;	The OLCs and emergency plan should be revised to reflect the results of the safety analysis.	The OLCs should be revised to: - Include periodic verification by measurements of the reactivity-shutdown margin, taking into account the relevant enveloping conditions of the proposed core configuration. - Include the list of radiation-monitoring equipment, their locations, and the associated alarm setting values, as well as the required actions in case of alarm triggering; - Establish technical and administrative requirements during prolonged shutdown periods; - Include periodic monitoring of the radioactivity load of the underground water using the existing sampling wells near the facility.
Management system for the operation phase;	/	- The contents of the operations cycle reports should be improved to include the necessary information that enables reactor management to verify the reactor's operational safety and to perform trending of the reactor's safety performance. - A procedure should be developed to evaluate postponed modifications before re-initiating work, taking into consideration the impact of subsequent modifications and experiments and need for re-approval. Similar considerations are valid for postponed experiments. Actions should be taken to reduce the accumulation of the reactor safety documents pending revision. The relevant management system process should be revised to make it easier for the document owners to revise them timely.
Maintenance, periodic testing and inspection, including ageing management activities	Monitoring of the reactor water leakage from the reactor pool, beam tubes, primary pumps and heat exchangers should be improved by installation of adequate an detection system.	The leakage rate and flow paths from the reactor pool should be determined, and adequate corrective actions should consequently be implemented to limit the water leakage.
Radiation protection;		Adequate radiation monitors for neutron dose should be installed in the beam tube area. It is suggested that an on-line stack monitor for aerosols, iodine, and particulates be installed.

9.5. Survey on the safety of research reactor

A Survey of the main EU Research Reactors used for Radioisotopes Production relative to their Safety status has been launched as part of the SAMIRA Study. The questionnaire (see appendix 16) has been sent to the main EU Research Reactors (BR-2 in Belgium, LVR-15 in Czech Republic, RJH in France, FRM-II in Germany, MARIA in Poland, HFR and PALLAS in Netherlands) producing radioisotopes.

The response rate has been low. Results are presented in the table below, but conclusions over the EU-28 cannot be drawn from these three RR surveyed.

Reactor Name	LVR-15	MARIA	PALLAS
Research Reactor Characteristics			
Radioisotopes produced	Mo-99	Mo-99, I-131 Lu-177, Ho-166	Mo-99, Y-90, I-125, Lu-177, Ho-166, Ir-192
Mo-99 weekly prod. Capacity	3000 Ci EOI	2100 6-day Ci EOI	at least HFR Capacity
Reactor Availability	30 weeks per year	35 weeks per year	>42 weeks per year
Mo-99 Availability	/	29 weeks per year	>42 weeks per year

Reactor Name	LVR-15	MARIA	PALLAS
Reactor Long-Term Operation (LTO)			
Design Lifetime	until 2028	/	> 40 years
Expected closing date	/	/	>2064
Last refurbishment	2014	2013	/
Operating License (OL) Validity	2020	2025	/
OL Expected Extension	Yes until 2028	Yes, until 2035	/
LTO Main challenges	Conformance to new safety standards and access to documentation	Identification of Ageing degradation effects, Equipment ageing Management	/
LTO Investment cost	€ 1-10 m	€ 1-10 m	/

Reactor Name	LVR-15	MARIA	PALLAS
Safety Regulation and Main Safety Issues			
Specific Regulation for RR	No	Yes	Yes
Main Safety Issues	Ageing Management Human Resources Safety Assessment	Ageing Management, Human Resources, Quality Assurance	Safety Assessment Human Resources Quality Assurance
Periodic Safety Review (SR)			
SR Frequency	Every 10 years (first in 2018)	Every 5 years	/

Last SR	2018	2017	/
	Safety Committee	INSARR Mission follow-up	
	Safety Analysis	Training and Qualifications	
Last SR Key Issues	Site Evaluation	Ageing Management	/
	Ageing Management	Activities	
	Activities	Utilisation and experiments	
	Utilization and experiments	Emergency Planning	
Dedicated Post-Fukushima SR?	Yes (scope limited)	Yes	/

Reactor Name	LVR-15	MARIA	PALLAS
Peer Reviews (PR)			
PR Details	2002 - INSARR	2014 – INSARR 2017 – INSARR Follow-Up Mission	/

Given the limited number of respondents, an official survey by the EC, relative to the implementation of Directive 2014/87, is recommended.

Nevertheless, the main findings of the survey show that some issues are shared by European Research Reactors and are fully consistent with IAEA observations on a worldwide basis:

- Research Reactors are facing ageing issues, especially as the vast majority of RR Operators expect to extend the Operating License;
- Main Safety Issues are linked to Safety Assessment, Human Resources, Quality Assurance and Ageing Management;
- INSARR Initiatives are the occasion of comprehensive Safety reviews;

BR2 publications shows, for instance, that Safety remains the foremost issue confronting operators in Europe. BR2 was subject to three 3 major periodic refurbishments: (1) 1979-1980; (2)1995-1997; and (3) 2015-2016 together with an Mo-99 capacity increase and Periodical Safety review in compliance with IAEA-SSG25. The budget for the last refurbishment was around EUR 50 million. During this latest refurbishment, the Beryllium matrix was replaced and the vessel inspected, stress tests were performed, followed by systems installation, some of them for protection against the consequences of severe accidents. As concerns long term operations, a formal methodological system for ageing management was developed, with an original inventory and classification of structures, systems and components and a maintenance strategy. Such approaches may constitute good practices to be shared by other European reactors. The new Beryllium matrix lifetime is expected to be 15-25 years. The next periodic safety review is forecast for 2026.

In the end, periodic safety reviews of the main European radioisotopes producing reactors, including INSARR missions, are performed every 5 to 15 years:

- HFR: 2016, 2011, 2005, 2002,
- BR2: 2016, 1999,
- LVR-15: 2018, 2003
- Maria: 2017, 2014 (NCBJ), 2000

10. Conclusion - recommendations

This study has evidenced the diversity of Health, Industrial and Research applications of ionizing radiation tools. This diversity and the fact that these tools are often embedded within equipment and services where their specific value is most often impossible to isolate, thereby making their economic impact difficult to evaluate reliably. However, their unique role for improving Health and for underpinning and enabling other technologies, products and services has been highlighted. A number of challenges remain to be overcome so Europe can derive maximum benefits from IR-based tools. For this purpose, a prerequisite is that these tools be considered as key applications.

The findings and the recommendations of the present study are summarized below.

	Findings and gaps	Recommendations
	Quality and Safety of widely disseminated technologies	
1	Computed Tomography: Dose reduction issue. According to COCIR, there are ~12000 CT scanners in Europe. One quarter of the CT installed base (3000 units) is deemed technologically obsolete and cannot be upgraded with the latest dose-savings technologies. This CT ageing installed base should be quickly renewed.	Assess the possibility of incentivizing all stakeholders, starting with private radiology practitioners. Compare the US situation (standard NEMA X-29, incentives for modernization) with the standards in force in Europe and make the necessary decisions when appropriate. Costing: The lifespan of a CT scanner is usually between 7-10 years. COCIR states that in Europe in 2016, 13% of CT units on average were older than 10 years, while 39% were 6-10 years old. With a typical 10% replacement rate, 3-4 years would be necessary to progressively replace old CT units from the 2000s. The standard cost range for "up-to-date" CT Scanner is EUR 0.5 m-EUR 1.3 m. Renewing equipment throughout the EU-28 would require an investment in the range of EUR 2-5 bn. Additional investments in terms of training, services would also be needed.
2	There is a threat to radiology personnel in Europe, which may lead to Quality and Safety concerns	Launching EU legislation covering teleradiology to: 1. Define teleradiology as a medical act in its own right. 2. Establishing EU-wide accreditation criteria for teleradiology providers. 3. Emphasizing the importance of ensuring high-quality health care delivery. 4. Applying international quality standards including monitoring service providers. 5. Regulating teleradiology as a responsibility of the member state where the patient undergoes the imaging procedure. 6. Full information of patients and informed consent about teleradiology usage.
3	Radiotherapy equipment is constantly being improved. The installed base should be renewed. Radiotherapy centres work organization and staffing are not harmonized in Europe, which may lead to Quality and Safety concerns	Costing elements: a. External X-Ray Radiotherapy (Intensity-Modulated Radiation Therapy) equipment cost range is EUR 2-3 m. b. Brachytherapy Unit ~EUR 0.5 m c. Particle Therapy centre (Proton, C-Ion or combined) ~ EUR 30-100 m. Concerning human resources and work organization in radiotherapy centres, assessing to what extent the BSS Directive is now being applied. Supporting the development of guidelines relative to human resources and radiotherapy departments organization. Such support might be in the form of a collaboration with national authorities and other

	Findings and gaps	Recommendations
		bodies, a communication to Health Authorities, an assessment of the impact of EU policies on these subjects or regular statistics and reporting on the size of inequalities in the EU and on successful strategies to reduce them. Supporting the ESTRO initiative to launch a type of Healthcare Technology Assessment of radiotherapy
4	Interventional radiology and radiation protection. Despite the completed actions to provide a clear framework for dose prevention in Interventional Radiology, results seem today quite uncertain.	A survey could be performed to evaluate the current state of the art and propose new actions from the public bodies to train medical workers on these issues. In parallel, epidemiological studies could be undertaken to clarify the suspicions between radiation exposition and induced cancer for medical workers.
5	Research Infrastructure: ESFRI's Neutron Landscape Group identifies and quantifies investment gaps. However, investment recommendations are not prioritised.	Pursuing investments in the ESS (European Spallation Source) to increase its number of instruments. Supporting the ESFRI Neutron landscape group initiatives for starting discussions between the funding agencies and neutron sources for defining a realistic investment plan.
6	Research Infrastructure/ Accelerators. The APAE issued recommendations in its 2017 Final Report, without costing the investments needed.	Inviting the APAE to quantify the requirements in terms of investment.
7	Consumer Products: they may represent a non-negligible market and are eliciting radioactive waste challenges. Policy relative to these products is not harmonized among MS.	Reiterating the 2007 RP146 A study: checking to see what progress has been made, evaluating the market better and deciding on further actions when/where appropriate.
EMERGING APPLICATIONS		
8	Protontherapy is developing. However, protontherapy treatment is more expensive than X-ray therapy and questions remain as to whether the additional patient benefit justifies the extra costs.	To resolve this issue, appropriate clinical studies are being conducted within EU Member States. Encouraging Member State collaboration through the establishment of a common framework approach for protontherapy clinical studies as well as launching studies and clinical trials aimed at broadening the clinical indications for proton therapy.
9	Nuclear medicine therapies are emerging. They potentially represent real progress towards personalised medicine and cost-savings for Healthcare systems. Obstacles to NM development should be addressed at the National and European levels.	- In the regulatory domain: increasing the development and dissemination of clinical guidance documents, including appropriate utilisation criteria. Improving understanding among those developing new radiotracers and radiotherapeutics as to what type of evidence is needed by the EMA and domestic Market Authorities to approve them as being safe, effective, reasonable and necessary. Communicate with EMA and National Market Authorities for regulatory approval of emerging agents that are safe and effective. Consistently support for the work that is being done in the field to promote greater understanding and support of NM/MI work before legislative and regulatory bodies. Fostering in-house labelling of imaging compounds. - Ensuring adequate and appropriate reimbursement for NM/MI procedures by the Healthcare reimbursement systems. Working with societies and agencies (including insurance) to optimize reimbursements of current and future agents. - In the education domain: increasing the reserve and

	Findings and gaps	Recommendations
		renewal of qualified personnel (practitioners, medical physicists, technologists, radiopharmacists, etc. to practice nuclear medicine. Increasing awareness of NM/MI as an appealing and rewarding field for students interested in STEM careers. - For the public: promoting greater understanding of radiation levels and benefits among the general public and in the medical field. - In the research domain: encouraging and promoting research in the field. As concerns the two latter points in particular, the opportunity of creating a European analytical campus, like those that exist for accelerators or neutron science, should be studied. Such a campus hinging around radioisotope production means and radiopharmaceuticals research labs would bring together all the other essential stakeholders to achieve efficient development of imaging and therapy compounds. As a prerequisite for convincing decision-makers, undertaking a solid Health Technology Assessment covering the emerging therapeutic applications in Nuclear Medicine now seems particularly opportune and is recommended.
	Medical radioisotopes : security of supply	
10	Research reactor based Mo-99 production will remain necessary to fulfil European and global demand until 2030. Significant decline in demand is not foreseen until 2030. A supply situation without a new dedicated research reactor in Europe – PALLAS being the most likely candidate – would not lead to European self-sufficiency and could create shortages at the global scale.	Consider an irradiation landscape in which PALLAS takes over the role of HFR as a reference scenario for the future of European irradiation capacity. For a sustainable renewal of the European research reactor radioisotope production capability, efforts towards Full Cost Recovery (FCR) at each step of the supply chain must be actively supported Closely monitor developments in cyclotrons as alternatives for future production capacity. Short-term solutions using alternatives are unlikely. Keep on monitoring the demand landscape – preferably by involving statistical bureaus and Eurostat. Costing elements: Diagnostic RI are either produced in Reactors (Mo-99/Tc-99m) or Cyclotrons (F-18), while Therapeutic RI are mostly produced in Research Reactors. The full investment cost of a cyclotron (Cyclotron, Facility cost, processing installations, etc.) is in the range of EUR 10-50 m, depending on the cyclotron characteristics (Beam Energy, current, Etc.). Multiple units may be needed to cover imaging RI needs in each country. The investment cost for a Research Reactor investment cost is in the range of EUR 300-500 m, while a RI processing facility is in the range of EUR 30-50 m.
11	Processing capacity does not seem problematic in the long term.	Support OECD NEA activities in monitoring global processing capacity.
12	For true European self-sufficiency, the production of research reactor fuel would need	Further investigate the economic and legal requirements for a production facility (see ESA currently updating its report)

	Findings and gaps	Recommendations
	to be secured.	Determine “flags”/indicators that would signal increased risk of supply shortages and appropriate planning periods for preparing investment and construction. Investigate the willingness to bear increased costs of Europe-produced fuel.
	Other applications	
13	Food irradiation	It is recommended that MS regulations in this area recognize the benefits of such techniques and that they be updated and harmonized (Directives 1999/2 & 3/EC and applicable domestic laws).
14	Sealed sources industrial applications	It is recommended to assess the current needs and imports volumes of RI for the industry sector across Europe with the support of each MS to evaluate EU dependency and conclude whether domestic supply should be fostered by EC.
15	Miscellaneous research	Starting for instance as of the ICARST 2017 papers, assessing the diverse ongoing research programmes and checking to see whether investment gaps exist in these areas in Europe.
	Spent Fuel and Radioactive Waste challenges	
16	Compared to the nuclear-energy industry, IR applications do not generate large amounts of radioactive waste (a majority of Healthcare Radioactive Wastes are handled through radioactive decay). However, MS reporting of information about non-energy waste strategies is uneven. Sealed sources, especially High activity sealed sources (HASS), are widely used in many fields and remain a waste concern.	Requesting that each MS report on how non-energy radioactive waste is adequately inventoried, packaged and collected, sorted, cleared or buried (VLLW), or stored (higher level or long-lived waste) in a dedicated installation, under close surveillance of an independent domestic body. Shared repository: This approach is currently being investigated by a European multinational working group established to study the feasibility of setting up a Development Organisation (ERDO) that would implement one or more shared geological repositories in Europe, with the support of the European Commission ²²² . Minor improvements to the HASS directive provisions (now replaced by 2013/59/Euratom) could be considered, including: i) specifying the “undue delay” for transferring disused sources from user premises to authorized bodies; ii) guaranteeing long-term knowledge about source design iii) providing financing guarantees to cover disposal costs. As concerns sealed sources, requesting that each MS follow a harmonized methodology for sealed sources inventory. Costing elements: - the largest interim storage facilities cost about EUR 200 m; - The typical investment for a geological disposal facility amounts to EUR 20-40 bn
	Safety Challenge: maintaining high safety levels for ageing Research Reactors	
17	As is true of other global research reactors, the main	An official survey by the EC, relative to the implementation of the 2014/87 Directive, is recommended.

²²²http://www.erdo-wg.com/erdo_news.html#15_05_2017.

	Findings and gaps	Recommendations
	safety issues for European research reactors are linked to ageing management (ageing-equipment management, access to old documentation, ageing of skilled-personnel, etc.), safety assessments & peer reviews, human resources, and quality assurance. The INSARR missions of the IAEA provide an essential tool to conduct independent Safety Evaluations/Peer Reviews. IR Technologies are a KET	Other EU ageing research-reactors operators could examine whether good practices can be derived from the approach developed by BR2 for the 2015/2016 reactor upgrade. Costing elements: As concerns Safety investments, costs are mainly due to periodic revamping of installations. A Research Reactor revamping cost is typically in the EUR 10-50 m range.
18	Despite their unquestionable role in improving Health, despite their economic impact and despite their underpinning a number of other technological and scientific progresses, ionizing radiation has not been retained among Key Enabling Technologies in the 2015 High Level Group on KETs Final Report: Time to Act. Cross-cutting challenges	Launching a study to substantiate and quantify the contribution of ionizing radiation technologies in each KET's development process: nanotechnology, micro- and nanoelectronics, including semiconductors, photonics, advanced materials, biotechnology, and advanced manufacturing technologies
19	In each domain of this study on Health, Industry and Research, experts stress the possible threat of skilled personnel.	Reiterating the 2012 EC/JRC study conducted about the Energy sector to cover the non-energy sector.
20	Reliable statistics are needed. Adequate decision-making is based on reliable figures. Many of the statistics related to ionizing-radiation applications, notably in Health, are unreliable or incomplete	With the support of MS, Eurostat to pursue the task of constituting reliable, homogeneous and standardized EU-28 databases in the domains addressed in this study, particularly in the Healthcare domain. In order to achieve this, convince MS of the importance of such reliable databases.

Please note: the figures given above are "order of magnitude" sums for potential investment costs, because prices depend on a number of parameters (equipment supplier, volumes, technology type, etc.).

Appendices

A1. Sealed and non-sealed radioactive sources applications

The sealed sources have been classified by the IAEA²²³. A list of the diverse sealed sources types is depicted below:

²²³ IAEA Tecdoc 1344 Categorization of radioactive sources



Table 25 : Sources types according to IAEA

On the above table, sources are sorted according to the IAEA classification²²⁴ based on the A/D (activity vs “danger” ratio). “D” characterizes the threshold Activity defined by IAEA from which source activity represents a danger to human health.

TABLE 1. Categorization table

Category	Categorization of common practices ^a	Activity ratio ^b (A/D)
1	Radioisotope thermoelectric generators (RTGs) Irradiators Teletherapy Fixed, multi-beam teletherapy (gamma knife)	$A/D \geq 1000$
2	Industrial gamma radiography High/medium dose rate brachytherapy	$1000 > A/D \geq 10$
3	Fixed industrial gauges -level gauges -dredger gauges -conveyor gauges containing high activity sources -spinning pipe gauges Well logging gauges	$10 > A/D \geq 1$
4	Low dose rate brachytherapy (except eye plaques and permanent implant sources) Thickness/fill-level gauges Portable gauges (e.g. moisture/density gauges) Bone densitometers Static eliminators	$1 > A/D \geq 0.01$
5	Low dose rate brachytherapy eye plaques and permanent implant sources X ray fluorescence devices Electron capture devices Mossbauer spectrometry Positron Emission Tomography (PET) checking	$0.01 > A/D \geq \text{Exempt}^c/D$

^aRecognizing that factors other than A/D have been taken into consideration (Section 2.3.6).

^bThis column can be used to determine the category of a source, based purely on A/D. This may be appropriate if, for example: the practice is not known or is not listed; sources have a short half-life and/or are unsealed; or sources are aggregated (See Section 3.3).

^cExempt quantities are given in Schedule I of the BSS [1].

Table 26 : IAEA categorisation of sealed radioactive sources

The International Source Suppliers and Producers Association (ISSPA) claims that the market of industrial radiography sources has a growth rate of 2-3% per year and that of sources for sterilisation industry, 5% [1]. Nevertheless, in France, IRSN, in charge of the national inventory of radioactive sources mentions a relative slowdown of the demand (private communication).

It seems that the actual trend of the industrial market for radioactive sources should be differentiated depending on the country and on the market segment. In industrial countries, which are already well equipped, the pressure of regulators, who require for each application a strict justification of the benefit brought by the use of a radioactive source with regards to alternative techniques, the slowdown can be understood. The situation may be different in developing countries, which have more massive needs of new equipment. On the other hand, the easiness of substitution of gamma emitters by X-ray electric sources or electron beams or even by methods free from use of any ionizing radiation source is different depending on the application.

In industry, sealed sources are used daily in the following industrial applications:

²²⁴ A/D ratio : A = characterizes the activity of each individual source of each radionuclide. D is an activity which characterizes the danger a source represents under certain scenarios and for certain dose criteria. A dangerous source is defined as: “A source that could, if not under control, give rise to exposure sufficient to cause severe deterministic effects.” See IAEA Tecdoc 1344 Categorization of radioactive sources.

- Non-destructive examinations (NDE)
- Materials processing
- Treatment of wastes, effluents and flue gas
- Different types of gauges

Radioactive tracers are used on a case-by-case basis, being injected in fluids for:

- Optimising industrial processes, including the study of dispersion of effluents
- Troubleshooting

NDE

Non-destructive examinations (NDE) are key techniques for some industries, most particularly nuclear manufacturing and construction, oil and gas and aeronautics. Even if their cost enters as a small fraction of the global cost of the final products, they are key enablers for allowing distribution of these products to their users: for nuclear reactors in particular, extensive inspections leading to precise identification and characterisation of possible flaws are requested before authorizing operation.

Status in nuclear energy

In nuclear industry gamma radiography is a key element of NDE techniques for heavy components in particular and their replacement by other techniques is not easy or even possible in some cases with the current status of technology. It is first a question of productivity, because many welds being circular, 360° panoramic radiography is much easier with an isotropic gamma source than with an X-ray source, which is directional. Moreover, pressure vessels and main ducts have very thick walls and high-energy radiation is required for screening possible defects deep inside these walls. The requirements of regulators for identifying smaller flaws, which were not detected in previous inspections, do not incite the nuclear industry to replace gamma radiography with X-rays, though regulators recommend such a replacement. It should be added that tomographic methods are strongly growing and produce very accurate results.

Nevertheless, the trend is more and more to replace the highest energy gamma sources by lower energy ones: Co-60 (1,17 and 1,33 MeV) by lower energy gamma sources, Ir192 (energy range from 206 to 612 keV) and Se75 (from 66 to 401 keV). This trend as well as the substitution of X-radiography with gamma radiography makes sense if at the same time progress is made in the sensitivity of detectors. The effort for reducing the energy of ionizing radiation used for massive industrial equipment makes sense only if it goes along with R&D on detectors to improve their sensitivity [2]. Already the use of numeric detectors improved sensitivity by a factor of 10, but there is still a great potential for improvements. Higher sensitivity of detectors cannot only result in more precise investigations, but they can contribute to improvements in productivity, as the same image quality will require a shorter exposure time.

Contrary to the use of gamma sources for controls in the workshop, where the source can be easily protected, the use of radioisotopes on site raises protection and security issues. Moreover, it limits productivity, as coactivity in the neighbourhood of a control performed with a radioactive source is not possible.

Now substitutes for ionising radiation are also considered. Ultrasound (US) can be an alternative in some cases, but its use for complex structures (e.g. LBM) and with some types of materials (cast iron, austenitic alloys) is very difficult because US diffusion is uneasy to forecast in such conditions. On the other hand, the use of new fabrication

techniques (HIP, additive manufacturing), allowing the manufacturing of more and more complex pieces, the control of which is uneasy, does not facilitate the use of US. There is nevertheless presently a H2020 project, ADVISE, for the development of ultrasound control methods for complex structures, but the opinion of experts is that in the short and medium term, the replacement of ionizing radiation by alternative methods will only be marginal and that in the domain of ionising radiation, gamma sources will still play a major role in a predictable future. Only limited slowdown of the demand of such sources can be expected.

Quantitative market elements

Quantitative elements relative to the EU-28 market of sealed or non-sealed sources could not be found. It is certainly difficult to perform a systematic annual data collection across the EU-28 like in Japan²²⁵. The latter reference provides nevertheless useful data like those reported in the table below such as quantifying the different uses of sources by users, by radioisotopes, etc., and could be taken as an example for Europe (see recommendation in §10.2).

機器 Appa- ratus 核種 Nuclides	総数 Total 構成比 (Ratio%)	非破壊 検査装置 Radio- graphy	厚さ計 Thickness Gauges	レベル計 Level Gauges	密度計 Density Gauges	水分計 Moisture Gauges	蛍光X線 分析装置 X-ray Fluorescence Spectrometer	スラブ 位置 検出器 Slab Position Detector	ガス クロマト グラフ Gas Chromato- graph	硫黄 分析計 Sulfur Meters	たばこ 量目 制御装置 Cigarette Weight controller	静電除去 装置 Electric Static Eliminator	ガス 検知器 Gas Detector	その他 Others	
総数 Total	34,421	100%	970	2,470	1,748	222	69	43	32	805	84	0	9	10	27,959
^3H	9,388	27.3	-	-	-	-	-	-	-	3	-	-	-	1	9,384
^{55}Fe	163	0.5	-	4	-	-	-	25	-	-	-	-	-	-	134
^{57}Co	273	0.8	-	-	-	-	-	-	-	-	-	-	-	-	273
^{60}Co	1,056	3.1	127	-	432	1	-	-	21	-	-	-	-	-	475
^{63}Ni	864	2.5	-	-	-	-	-	-	-	802	-	-	-	9	53
^{68}Ge	114	0.3	-	-	-	-	-	-	-	-	-	-	-	-	114
^{85}Kr	11,242	32.7	-	1,246	-	3	-	-	-	-	-	-	-	-	9,993
^{90}Sr	134	0.4	-	133	-	1	-	-	-	-	-	-	-	-	-
$^{119\text{m}}\text{Sn}$	76	0.2	-	-	-	-	-	-	-	-	-	-	-	-	76
^{137}Cs	2,494	7.2	20	273	1,316	134	-	-	11	-	-	-	-	-	740
^{147}Pm	343	1.0	-	202	-	-	-	-	-	-	-	-	-	-	141
^{153}Gd	1	0.0	-	-	-	-	-	-	-	-	-	-	-	-	1
^{170}Tm	2	0.0	2	-	-	-	-	-	-	-	-	-	-	-	-
^{192}Ir	740	2.1	740	-	-	-	-	-	-	-	-	-	-	-	-
^{204}Tl	1	0.0	-	1	-	-	-	-	-	-	-	-	-	-	-
^{210}Po	13	0.0	-	-	-	-	-	-	-	-	-	-	5	-	8
^{241}Am	1,850	5.4	2	581	-	83	2	5	-	84	-	-	-	-	1,093
$^{241}\text{Am/Be}$	60	0.2	-	-	-	-	60	-	-	-	-	-	-	-	-
^{252}Cf	4	0.0	-	-	-	-	4	-	-	-	-	-	-	-	-
Others	5,603	16.3	79	30	-	-	3	13	-	-	-	4	-	-	5,474

*表示付認証機器は含まれていない。
医療機関における装置機器等は含まれていない。
*Number of approved devices with certification labels are not included.
Also major apparatus used in Hospitals and Clinics are not included.

Table 27: Sources in Japan, sorted by use and radioisotope

²²⁵ Statistics on the use of Radiation in Japan, 2016

Procurement of sources

There are several steps in the procurement of radioactive sources until they reach the end-users in charge of industrial applications of these sources:

- The production of radioisotopes, which is performed in reactors (mostly research reactors) or in accelerators (cyclotrons or linear accelerators). It should be noted that it is not the same radioisotopes that can be produced by these two means: accelerator produced radioisotopes are typically neutron deficient, while radioisotopes produced in reactors have an excess of neutrons.
- The processing of the irradiated targets
- The conditioning of radioisotopes
- The distribution of sources
- For sealed sources, their integration into devices that will be used for various applications, which may include the addition of an electronic and mechanical environments adapted to each application.

Different industrial players are generally in charge of implementing these steps.

Production of radioisotopes

The variety of radioisotopes used in industry is rather large. For instance, reference [4] lists 18 radioisotopes used for a scope limited to NDT, gauges, sterilization and some tracing applications. As it can be seen in the following table, apart from 4 of them. Am-241, Au-198, Co-60, Cs-137, all other radioisotopes are used for a single type of application. Some being also at the utmost importance for brachytherapy and external radiation therapy (Ir-192, Co-60...).

	Ag110m	Am241	Au198	Co60	Cs137	H3	Ir-192	La140	Kr85	Mn54	Ni63	Sc 46	Se75	Sr90	Tc-99m	Ti204	Yb169	Zn65
Miscellaneous gauges																		
Density measurement																		
Fill height detector																		
Smoke detector																		
Ash content of coal																		
Sterilisation																		
Residence time in blast furnace																		
Industrial radiography																		
Tracing of pollutants																		

Figure 50: Radioisotopes use in the Industry

A limited market is therefore expected for each of them.

In 2008, the US-DOE pointed out the fact that there was no more domestic production for many radioisotopes needed for medical, industrial and research applications. In particular the very varied radioisotopes required for industrial and research applications were mostly produced in Russia and the unreliability of this supply was underlined [5]. In 2011, the effort for restoring national production capacity was described in a USDOE paper [6]. It seems to have produced significant results [7]. The situation improved significantly in terms of availability of radioisotopes, but the cost effectiveness of the solutions considered for domestic supply does not seem to be consolidated yet.

In Europe, it appears that such a systematic approach has not been undertaken until now and it seems that a large part of the radioisotopes required by industry is still coming from Russia or Canada. It is recommended to assess whether domestic supply should be fostered by EC (see recommendation in §10.2). In relation to the size of the market, this dependence seems not to raise strategic concerns, but as already mentioned above, it should be considered that some uses of radioisotopes play the role of enablers in strategic domains like energy and that, for some applications, their replacement cannot be envisaged, at least in the short and medium term.

- [1] "Role of Industry in Long-term Management of Disused Radioactive Sealed Sources" – Paul Gray, Chairman ISSPA, IAEA Workshop on Cradle to Grave Control System, Vienna, March 2017
- [2] "Industrial Applications of Radioisotopes and Radiation Technology and Agency's Role" – N. Ramamoorthy, M. Haji-Saeid, IAEA, Third Eurasian Conference Nuclear Science and its Applications, Taschkent, October 2004
- [3] <http://www.fanc.fgov.be/fr/page/doi-3-tihange-2-flaw-indications-in-the-reactor-pressure-vessel-steel/1989.aspx>
- [4] <http://www.etf.com/sections/features-and-news/2095-radioisotopes-a-market-in-decay?>
- [5] Workshop on The Nation's needs for Isotopes: Present and Future – US Department of Energy, Office of Science, Rockville, August 2008
- [6] https://science.energy.gov/~media/np/nsac/pdf/mtg%203211/NSAC_isotope_0311.pdf
- [7] Meeting isotope needs and capturing opportunities for the future: the 2015 long range plan for the DOE-NP Isotope program – DOE/NSF Nuclear Science Advisory Committee, July 2015

A2. Computed Tomography (CT)

A.2.1. General Principle

A CT scan makes use of computer-processed combinations of many X-ray measurements taken from different angles to produce cross-sectional (tomographic) images (virtual "slices") of specific areas of a scanned object.

Computed tomography operates by using an X-ray generator that rotates around the target; X-ray detectors are positioned on the opposite side of the circle from the X-ray source. Once the scan data have been acquired, the data must be processed using a form of tomographic reconstruction, which produces a series of cross-sectional images, that can be assembled to create a 3D model.

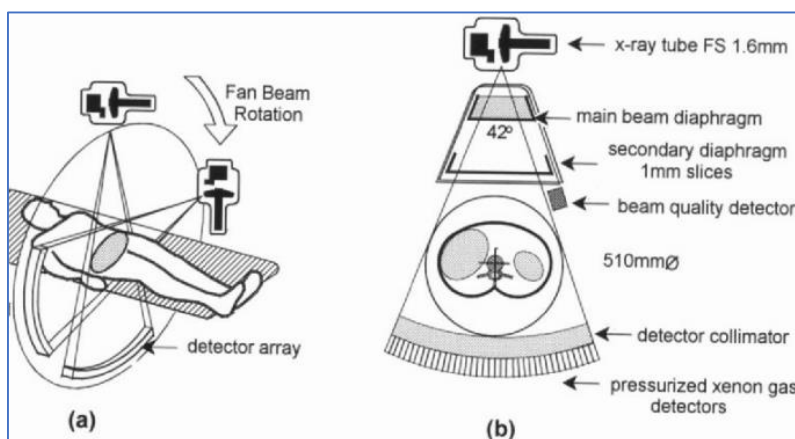


Figure 51: Typical 3rd generation CT Scanner principle

In terms of clinical indications, CT is well suited for bone injuries, lung and chest imaging, cancer detection and is widely used on Emergency Room patients²²⁶, whereas MRI (its main alternative) is more suited for soft tissue evaluation, (e.g., ligament and tendon injury, spinal cord injury, brain tumours, etc.).

A.2.2. Computed Tomography Situation in the EU

The following data are extracted from Eurostat (July 2017) and RP180 (2012 data). There were around 55 million exam CT in 2015 in EU (against about 45 million in 2010)²²⁷. It corresponds to a 30% increase over 5 years (an average of 4% per year). The following graph uses only the data for certain countries²²⁸ for which Eurostat data are available.

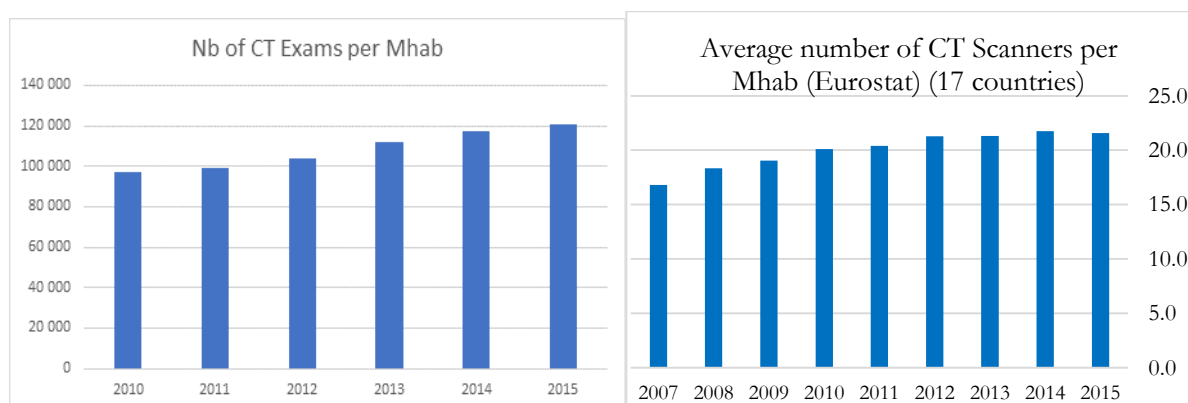


Figure 52: Eurostat statistics on CT equipment availability and use

²²⁶ French Radiology Society study "Accès aux examens d'imagerie médicale en urgence" CT exams are 6 times more prescribed by Emergency Services than MRI;

²²⁷ Data from Eurostat extrapolated over EU-28 – 96% of EU-28 population coverage ;

²²⁸ BE, CY, CZ, DE, DK, EE, ES, FI, FR, HU, LT, LU, LV, NL, RO, SI, SK;

The above averaged data seem coherent with the COCIR data per MS below.

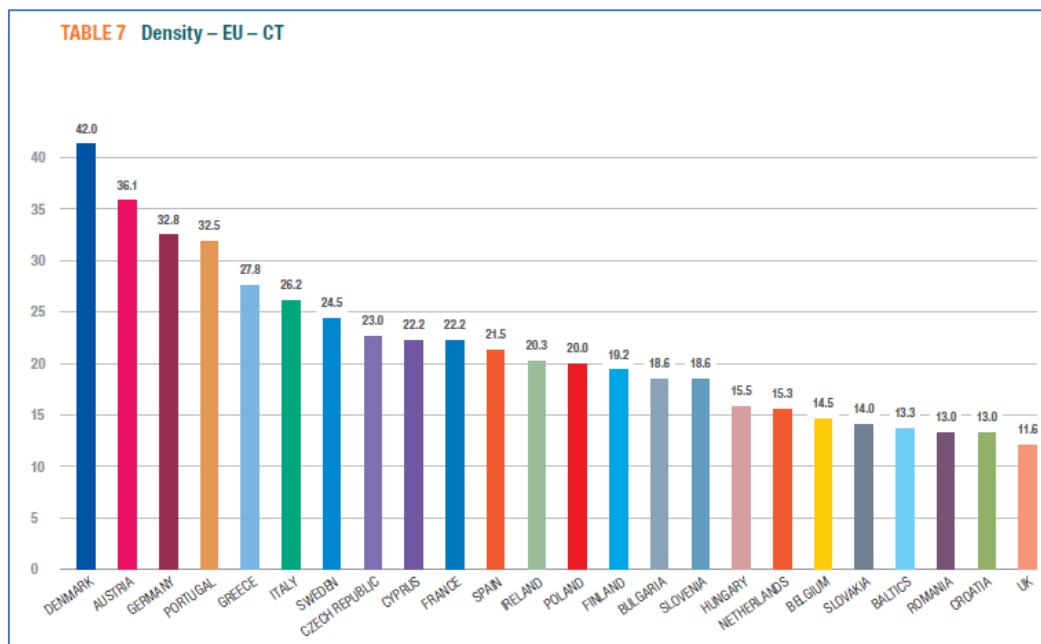


Figure 53: CT density (Equipment per MHab) for EU Countries - Source COCIR

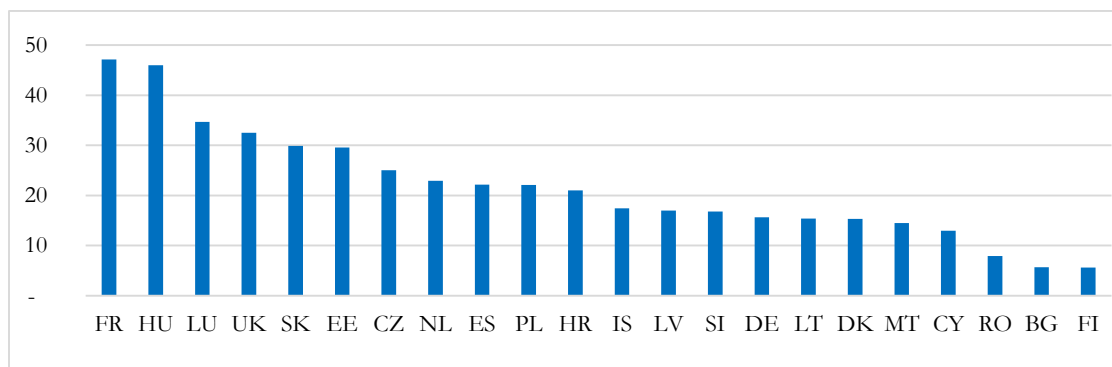


Figure 54 : Frequency of CT exams / equipment / day in EU (Assumption: 5 days/wk use)

There were around 22 CT Scanners per Millions of persons in 2015, with an increasing rate of about 2% per year. On average, 21 exams are performed per scanner and per working day (with an assumption of 5-days/wk use). Large discrepancies in terms of CT exams frequency per MHab exist between EU-28 countries and no direct correlation was found between equipment density and exams frequency.

The issue of public doses

The figure below shows that CT and Radiography (to a lesser extent) are the major contributors to the average dose received by the population in Europe.

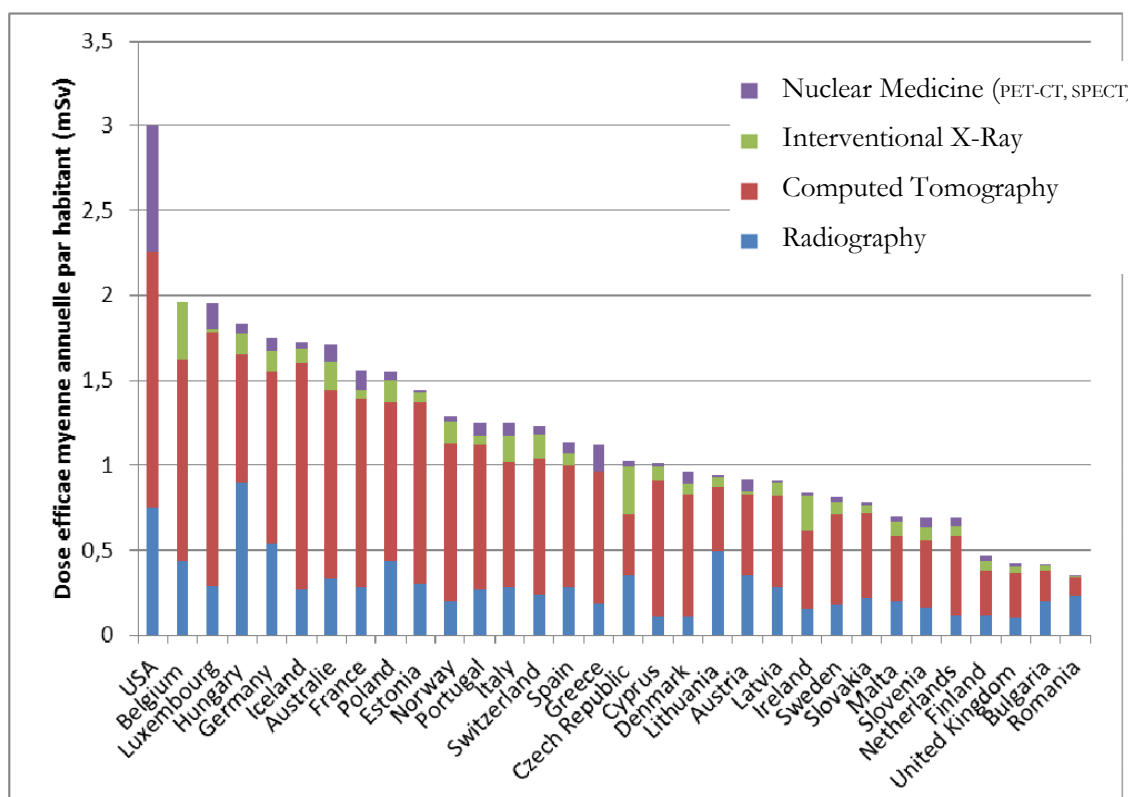


Figure 55: Yearly Average dose received (mSv) per Habitant for Diagnostic Applications in 2012 – Source: IRSN Exposition de la population française aux rayonnements ionisants liée aux actes de diagnostic médical en 2012

According to these data, doses are very variable within EU-28 MS. In addition, large variations of the average received dose by patients per CT procedure type can be observed among EU MS according to RP180 study gathered data:

Country	CT head	CT neck	CT chest	CT spine	CT abdomen	CT pelvis	CT trunk
MEAN	1,92	2,52	6,56	7,72	11,3	7,26	14,8
MAX	3,98	5,38	20,4	16,3	28,7	14,5	50,5
MIN	0,28	0,42	2,0	2,4	2,6	0,80	2,4
MAX/MIN	14,3	13,0	10,0	6,9	11,0	18,1	21,5

Figure 56 : The typical effective doses (mSv) estimated in European countries for computed – RP180

For the same examination, dose received can vary up to a factor of 10 to 20 depending on the country where the CT scan is performed. Such variations can be related to equipment characteristics (technology and age), clinical indications and “good practices” used.

Achieving dose reduction necessitates first awareness of the various stakeholders, such as clinical professionals, equipment manufacturers, regulators, hospital managers, patients, etc. in order new requirements and the implementation of future workflow

concepts on dose management and dose reporting can be implemented around the world.

In the next paragraphs, details are provided upon

- i) CT technical evolutions, both short-term and long-term,
- ii) COCIR/HERCA initiatives and
- iii) other challenges to be faced.

A.2.3. Computed Tomography –latest technical evolutions

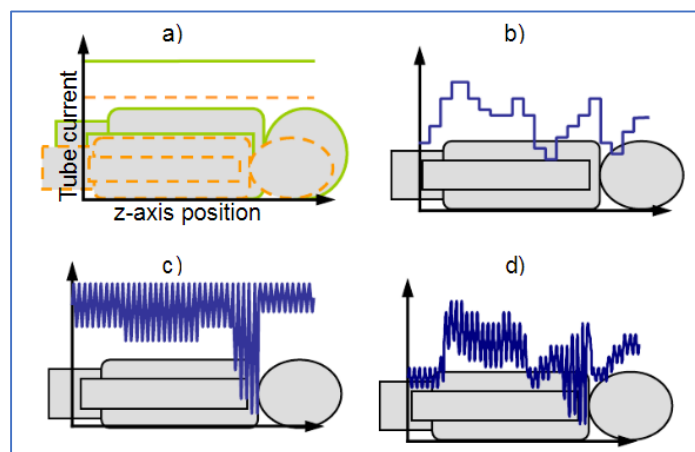
CT radiation dose optimization is an important concern to lower the associated population risks. Several efforts have been taken in the last decade by the imaging community to reduce the dose to as low as reasonably achievable (ALARA). Scanner manufacturers have contributed with the development of technologies reducing doses while maintaining image quality, such as automatic exposure control (AEC) or iterative reconstruction. Their professional institution COCIR has also taken numerous initiatives, presented below.

A.2.3.1. Dose reduction techniques

Automatic Exposure Control

The usual method for adjusting exposure levels in CT is to adjust the tube current or rotation time. This control can be used to adjust the beam to the patient morphology, to the body section under examination (*the beam intensity would be relatively low through the thorax region, which is less attenuating due to the presence of the air-filled lungs, and higher through the abdomen, which is denser*) and to the beam angular variations.

AEC systems by themselves do not automatically lead to a reduction in patient dose. However, when used correctly, their use generally tends to result in reduced doses.



a) patient size AEC: higher mA is used for larger patient, b) z-axis AEC: higher mA used at more attenuating z-axis positions, c) rotational AEC: the degree of modulation depends on asymmetry at each z-axis position

Figure 57: Three levels of Automatic exposure control

Iterative reconstruction

Iterative reconstruction techniques have the potential to enable CT radiation dose optimization by either lowering tube current or tube voltage.

The figure below gives a schematic representation of the principle of iterative image reconstruction algorithms. Following the CT acquisition process (measured projections), a first image estimate is generated. An x-ray beam is simulated via forward projection to obtain simulated projection data, which are then compared with the measured projection data. In case of discrepancy, the first image estimate is updated based on the characteristics of the underlying algorithm. This correction of image and projection data is repeated until a condition predefined by the algorithm is satisfied and the final image is generated.

Each vendor developed its own iterative reconstruction tool and estimated the dose saving reduction up to 80%. Dose reduction is highly dependent on the body area investigated (head and neck²²⁹ – 20 to 40% dose reduction achievable, urography – 45 to 84% dose reduction achievable, routine chest CT – up to 75% dose reduction²³⁰...).

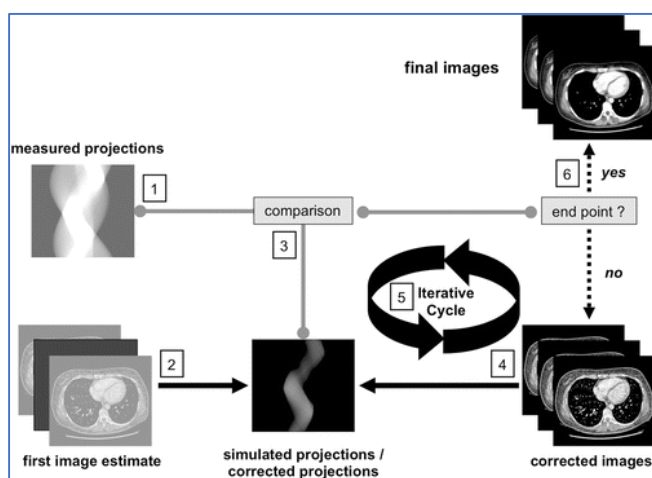


Figure 58: Iterative reconstruction principle

A.2.3.2. CT future technological perspectives: “photon counting detectors”

All current commercial CT systems use scintillator photo diode detectors (See Figure A). They comprise scintillators that are individually cut and polished, coated with reflectors to prevent crosstalk between cells, and optically coupled to photo diodes. X-rays absorbed in the scintillator produce light that is converted by the photodiode into an electrical signal.

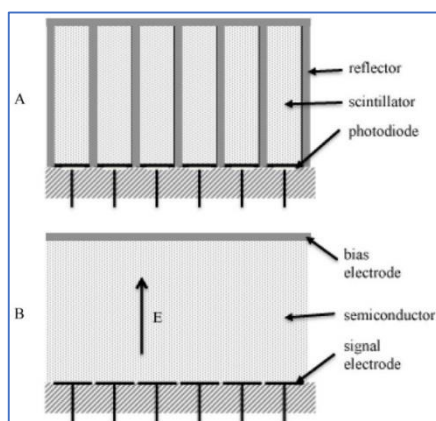


Figure 59 Difference between scintillator photo diode detectors and direct conversion photon counting detectors for CT systems

²²⁹ State of the Art: Iterative CT Reconstruction Techniques Lucas L. Geyer, MD
<http://pubs.rsna.org/doi/abs/10.1148/radiol.2015132766>

²³⁰ CT Radiation Dose and Iterative Reconstruction Techniques
AtulPadole <http://www.ajronline.org/doi/full/10.2214/AJR.14.13241>

With Direct conversion photon counting detectors (see Figure B), each photon creates a number of charge carriers in the semiconductor in proportion to the energy deposited. Crosstalk between adjacent detector channels is prevented by the fact that the charge carriers produced in the semiconductor follow electric field lines, so these detectors do not require reflectors to avoid significant crosstalk. If the electronics are designed so that individual photons are detected and counted, the system can avoid the electronic noise problem. A threshold sufficiently higher than the electronic noise floor is defined so that any x-ray photon that produces a signal whose height exceeds the threshold is converted to a digital event; the electronic noise is no issue other than setting a lower limit on the energy of the x-rays that can be detected.

Initial studies show that photon counting detectors could bring an additional dose reduction of 30-45%^{231,232} compared to standard CT systems detectors. Research on this technology should be supported to accelerate its development and enable large dose decrease for the next generation of CT equipment. For instance, a 4-year collaborative European Project led by the "Université Claude Bernard Lyon 1" was selected and granted 6.4 M€ under the "Horizon 2020" European Research and Innovation program. The Spectral Photon Counting CT European Project using a unique Philips prototype involves 11 European partners and will last 48 months from January 2016 to December 2019.

A.2.4. Dose reduction: COCIR initiatives²³³

Since February 2010, regular discussions are taking place between COCIR and the Heads of European Radiation Competent Authorities (HERCA) requesting the industry to commit in reducing radiation dose for CT equipment. As the developers of sophisticated scanners, CT manufacturers acknowledge their unique role in the process to help optimize patient CT dose in the health care setting, a dedicated COCIR Task Force was created to respond to HERCA's request and a COCIR CT manufacturers' voluntary commitment was released in May 2011.

The aim of this commitment is to further the initiatives of improving dose reporting, promoting transparency in dose efficacy, continuing reduction of medical exposures, and provision of specific training curricula.

The manufacturers have agreed to complete the voluntary commitments outlined within and provide yearly updates on:

1. Characterization of CT Systems Standardized Benchmarking
2. Implementation of dose reduction measures in CT
3. Dose management and reporting
4. Provision of specific training curricula

COCIR CT manufacturers have been developing and providing dose reduction features on CT systems for many years, and this trend continues today:

²³¹ S. Kappler et al., First results from a hybrid prototype CT scanner for exploring benefits of quantum-counting in clinical CT, Proc. SPIE 8313, pp. 83130X (2012).

²³² Radiation dose reduction in computed tomography: techniques and future perspective - Lifeng Yu

²³³ Self-regulatory initiative for Medical imaging equipment Status Report 2016. COCIR

- Patient protocol selection Guidance
- Automatic tube current modulation (ATCM) and X-ray initiation
- Precise X-ray field shaping
- Dose efficient design
- Dose reporting and awareness
- Training opportunities
- Pediatric protocols
- Dedicated infant imaging mode
- Advanced tube and collimator design
- Dose efficient detection
- Dose display and recording
- Optimized image reconstruction

All the documentation related to the COCIR Voluntary Commitment with HERCA is available on the COCIR website. HERCA issued recently (November 2017) a positive conclusive paper²³⁴ about their collaboration with COCIR members.

A.2.4.1. Computed Tomography – future challenges

Based on last decade continuous increase trend of CT, it is more than likely that the CT use will continue to grow in the next years, it is therefore essential to regulate its use, as CT is currently the main dose contributor of European average dose per habitant.

Equipment manufacturers are aware of the need to reduce the doses coming from CT, however, numerous other stakeholders intervene on this question. After technology evolution, the question of equipment renewal comes next. In mid-2016, there were over 5000 CT systems operating world-wide with iterative reconstruction technology²³⁵, representing less than 10% of global worldwide CT installed base²³⁶. COCIR has evaluated the age breakdown of CT equipment through EU. It shows that an important number of equipment are in use for more than 10 years: these equipment do not benefit of the most recent optimization in terms of dose modulation or iterative reconstruction.

²³⁴CT Manufacturers Stakeholder Involvement (HERCA Report).

<http://www.herca.org/uploaditems/documents/171115%20-%20HERCA%20COCIR/CT%20manufacturer%20involvement%2022-11.pdf>

²³⁵ Iterative Reconstruction in CT: What Does It Do? How Can I Use It? William P. Shuman, MD, FACR, FSCBTMR, FSCCT University of Washington School of Medicine, Seattle, WA

²³⁶ [60k CT equipments estimated in 2015 – 2011 Estimate]

http://www.prweb.com/releases/computed_tomography/ct_scanners/prweb8075828.ht

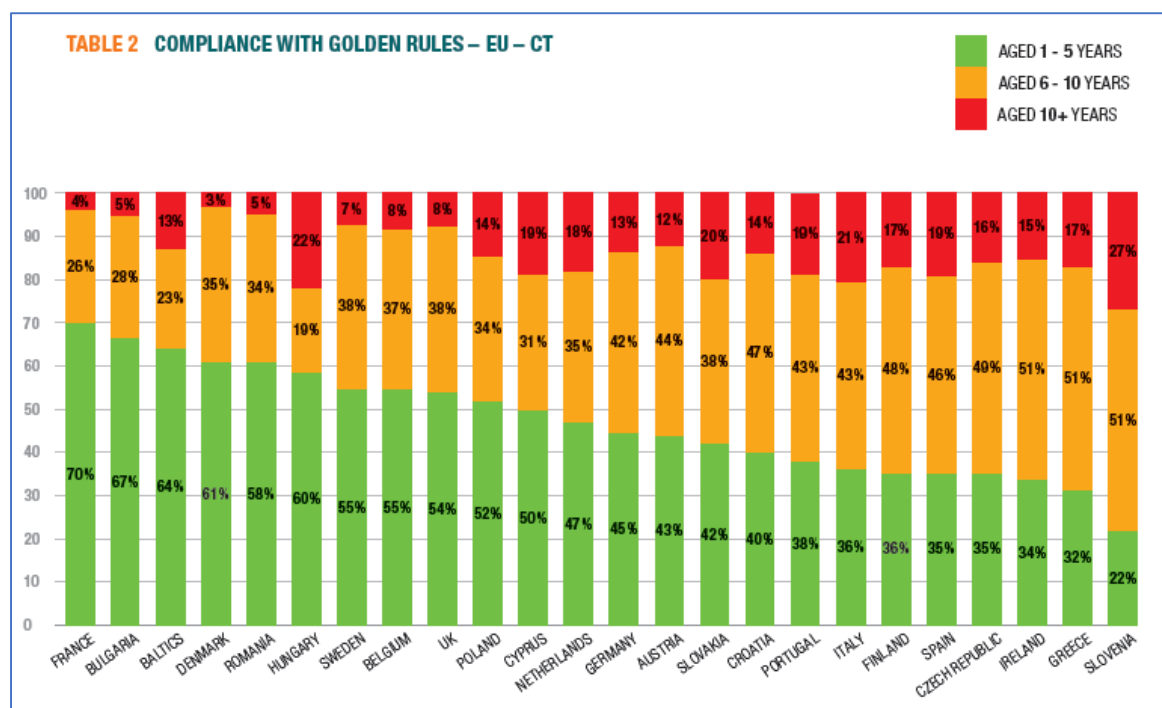


Figure 60: Age distribution of CT equipment among EU - source COCIR

Technical evolution of computed tomography equipment/tools can drastically reduce the dose received by the patients but is a challenge for the medical world which has to digest the constant improvements coming from the industry, and for the “payers” who have to replace obsolete equipment. USA has taken radical measures on this subject.

Beyond that, in the last few years, different studies evidenced that an important number of CT exams performed are not needed or could be replaced by others imaging acts:

1. Study by the American College of Cardiology Foundation (ACCF) and United Healthcare found that 14% of the CT exams were inappropriate and 15% were of “uncertain appropriateness.”²³⁷
2. Study found that nearly 30% of Medicare beneficiaries with uncomplicated lower back pain received an imaging service within 28 days, even though imaging is rarely indicated in the absence of complications.²³⁸
3. Another study²³⁹ found that more than 50% of abdominal CT scans may be unnecessary

Such excessive CT prescriptions can be due to different reasons:

1. The lack of communication between medical centres forcing them to duplicate exams;
2. Patient expectations, as CT exams have become usual in the public opinion;
3. Doctors precautions, which may prefer to prescribe nearly useless exams rather than risk being sued for negligence;
4. The difficulty to follow the fast evolution of imaging technologies.

²³⁷ Robert C. Hendel, MD, Manuel Cerqueira, MD, et al, "A Multicenter Assessment of the Use of Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging with Appropriateness Criteria," Journal of the American College of Cardiology, 2010, 55(2): pp. 156-162.

²³⁸ Hoangmai H. Pham, MD, MPH, Bruce E. Landon, MD, MBA, et al, "Rapidly and Modality of Imaging for Acute Low Back Pain in Elderly Patients," Archives of Internal Medicine, 2009, 169(10): p. 972.

²³⁹ Kristie M. Guite, MD, J. Louis Hinshaw, MD, et al, "Ionizing Radiation in Abdominal CT: Undiagnosed Multiphase Scans are an Important Source of Medically Unnecessary Exposure," Journal of the American College of Radiology

Back in 2014, the US President signed the Protecting Access to Medicare Act. According to this act, the Centres for Medicare & Medicaid Services (CMS) will reduce their reimbursements for certain diagnostic procedures performed with CT equipment that does not meet a certain CT standard²⁴⁰. Starting in 2016, the reimbursement penalty is 5 percent, but for 2017 and onwards, the penalty would increase to 15 percent. To avoid the reimbursement cut, a compliant CT scanner needs four attributes²⁴¹ designed to optimize, reduce, and document dose radiation without affecting the quality of diagnostic imaging.

These difficult questions echo the 2012 Bonn Call for Action to Improve Radiation Protection in Medicine in the next decade stating that the “awareness, assessment, audit” attitudes and practices of the medical sector from the radiation protection point of view are the key issues.

²⁴⁰ <http://www.providianmedical.com/blog/xr-29-compliance-ct-scanners>

²⁴¹ The four attributes are : Automatic Exposure Control (AEC), Reference Adult and Pediatric Protocols, CT DICOM Radiation Dose Structured Reporting (RDSR) & MITA Smart Dose Check.

A3. Interventional Radiology

Interventional radiology using X-rays, such as fluoroscopy, is the method that provides real-time X-ray imaging that is especially useful for guiding a variety of interventional procedures. For patients, the risk of a cancer from the exposure is not a major concern when compared to the benefits of the procedure. However, medical staff must be careful of the risks related to indirect radiation exposure (radiation-induced cataract, cardiovascular diseases, etc.). Doses are likely to be higher when these procedures are performed with fluoroscopic equipment that lacks state-of-the-art dose-reduction features or by operators who lack adequate training in radiation protection.

Radiation dose is affected by the complexity of the procedure, the patient, the operator, and the equipment. This doesn't just concern the patients; the operator and staff also need to be monitored. For example, an operator with a workload of four procedures per day could be exposed to an annual dose of 10 mSv to 450 mSv to the neck, 10 mSv to 550 mSv to the eye lens (*where BSS dose limit is 20 mSv per year, averaged over 5 consecutive years, and 50 mSv in any single year*), and 30 mSv to 640 mSv to the hand²⁴² (*where BSS dose limit is 500 mSv equivalent dose per year to the extremities (hands and feet) or to the skin*). Two of the main radiation-induced effects and risks to Interventional Cardiologists and Other Medical Staff are summarized below:

1. One of the most vital yet ill-defined effects associated with ionizing radiation exposure is the effect on the transparency of the eye lens, a pathology called radiation cataract²⁴³. Occupational exposure to ionizing radiation and lens opacities has been reported for medical personnel, such as radiology technicians. Earlier studies have demonstrated a significant increase in eye lens opacities among interventional cardiologists and medical staff in cardiac catheterization laboratories²⁴⁴. Later reports based on experiences from different countries indicated that risk of lens opacities among interventional cardiologists was at least twice that of unexposed groups²⁴⁵. Further research is needed to focus on interventional cardiologists regarding radiation exposure²⁴⁶ and development of cataracts.
2. Increased risk of cardiovascular diseases associated with ionizing radiation has received recent attention. Several studies have demonstrated the effects of ionizing radiation on hematologic parameters and immunologic function; however, the question of whether radiation affects other physiologic phenomena, including arterial blood pressure, is still under debate despite continuous research efforts. Data on the association between chronic low dose radiation and cardiovascular diseases are currently limited. Epidemiological studies are needed to help clarify

²⁴² http://www.auntminnie.com/index.aspx?sec=rca&sub=ecr_2016&pag=dis&ItemID=113650

²⁴³ Radiation-Induced Noncancer Risks in Interventional Cardiology: Optimisation of Procedures and Staff and Patient Dose Reduction - Zhonghua Sun, AiniAbAziz, and Ahmad KhairuddinMdYusof

²⁴⁴ E. Vano, N. J. Kleiman, A. Duran, M. M. Rehani, D. Echeverri, and M. Cabrera, "Radiation cataract risk in interventional cardiology personnel," *Radiation Research*, vol. 174, no. 4, pp. 490–495, 2010.

O. Ciraj-Bjelac, M. M. Rehani, K. H. Sim, H. B. Liew, E. Vano, and N. J. Kleiman, "Risk for radiation-induced cataract for staff in interventional cardiology: is there reason for concern?" *Catheterization and Cardiovascular Interventions*, vol. 76, no. 6, pp. 826–834, 2010.

²⁴⁵ S. Mrena, T. Kivelä, P. Kurttio, and A. Auvinen, "Lens opacities among physicians occupationally exposed to ionizing radiation - a pilot study in Finland," *Scandinavian Journal of Work, Environment and Health*, vol. 37, no. 3, pp. 237–243, 2011.

O. Ciraj-Bjelac, M. Rehani, A. Minamoto A et al., "Radiation-induced eye lens changes and risk for cataract in interventional cardiology," *Cardiology*, vol. 123, pp. 168–171, 2012.

²⁴⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4628470/>

the possible mechanisms between radiation exposure and its effect on the micro-cardiovascular damage.

EC is mobilized on these radiation protection issues for medical workers, through various initiatives:

- ORAMED²⁴⁷, Optimization of RAdiation protection for MEDical staff is a collaborative project funded in 2008 within the 7th EU Framework Programme and aims at the development of methodologies for better assessing and reducing exposures to medical staff for procedures resulting in potentially large doses or complex radiation fields, such as interventional radiology, nuclear medicine and new developments;
- PROCARDIO²⁴⁸, that aims at improving understanding of the risks of cardiovascular disease at low doses;
- Seminars²⁴⁹, such as recent one in 2017 on radiation protection has been dedicated to “Emerging issues with regard to organ doses”.

Effective dose reduction outcomes having been achieved. These include strategies of dose monitoring during the procedure, wearing protective devices, applying dose-reduction techniques, and implementing training and education programmes.

On this last point, the European Commission²⁵⁰ and ICRP²⁵¹ (International Commission on Radiological Protection) have addressed the importance of training in radiological protection, publishing guidelines with specific recommendations for training programmes for interventional procedures²⁵². However, recent surveys show that radiation protection knowledge for non-radiologist staff remain heterogeneous²⁵³ and need to be improved.

Despite the completed actions to provide a clear framework for dose prevention in Interventional Radiology, results seem today quite uncertain. A survey could be performed to evaluate the current state of the art and propose new actions from the public bodies to train medical workers on these issues.
In parallel, epidemiological studies could be undertaken to clarify the suspicions between radiation exposition and induced cancer for medical workers.

²⁴⁷ <http://www.oramed-fp7.eu/>

²⁴⁸ https://cordis.europa.eu/result/rcn/170991_en.html

²⁴⁹ <https://ec.europa.eu/energy/en/radioactivity-seminars>

²⁵⁰ Radiation protection no 175, Guidelines on radiation protection education and training of medical professionals in the EU <https://ec.europa.eu/energy/sites/ener/files/documents/175.pdf>

²⁵¹ E. Vano, M. Rosenstein, J. Liniecki, M. Rehani, C. J. Martin, and R. J. Vetter, “ICRP publication 113: education and training in radiological protection for diagnostic and interventional procedures,” *Annals of ICRP*, vol. 39, 2009.

²⁵² The European Commission and ICRP have addressed the importance of training in radiological protection, publishing guidelines with specific recommendations for accreditation of training programmes for interventional procedures. ICRP Publication 113 recommends that training in radiological protection is included in the quality assurance programme, with special attention to training given to fellows and residents. The guideline provided by European Commission suggests specific learning objectives and 20–30 hours of training for interventional cardiologists. Much effort has been made over the last decade to produce training materials to help improvement of radiation protection in interventional cardiology procedures, with successful outcomes having been achieved. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3762166/>

²⁵³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4337119/> Evaluation of non-radiologist physicians' knowledge on aspects related to ionizing radiation in imaging

A4. Human resources challenge

A.4.1. Demographic Radiologist challenge in the EU

Large discrepancies exist between Western European countries in terms of practising radiologists (from 4.7 in UK to 12 in France per 100k habitants), but every country faces the same challenge: the slowly-growing number of radiologists compared to the fast-growing use of CT, MRI and CR²⁵⁴ should lead to a progressive lack of radiologists.

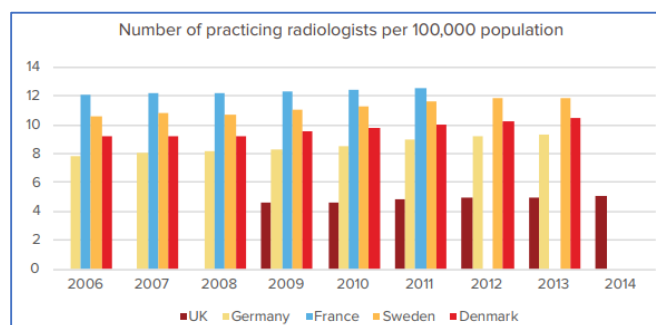


Figure 61: Number of practicing radiologists per 100,000 population – Source EUROPE'S LOOMING RADIOLOGY CAPACITY CHALLENGE A COMPARATIVE STUDY - C. SILVESTRIN - TMC

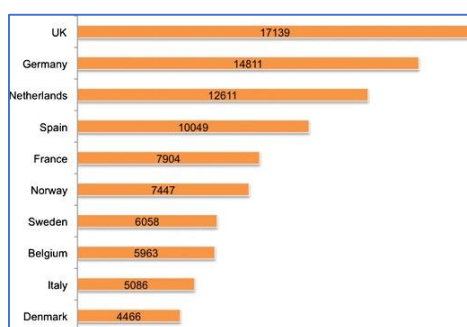


Figure 62: Number of Habitants per Radiologists in different EU countries

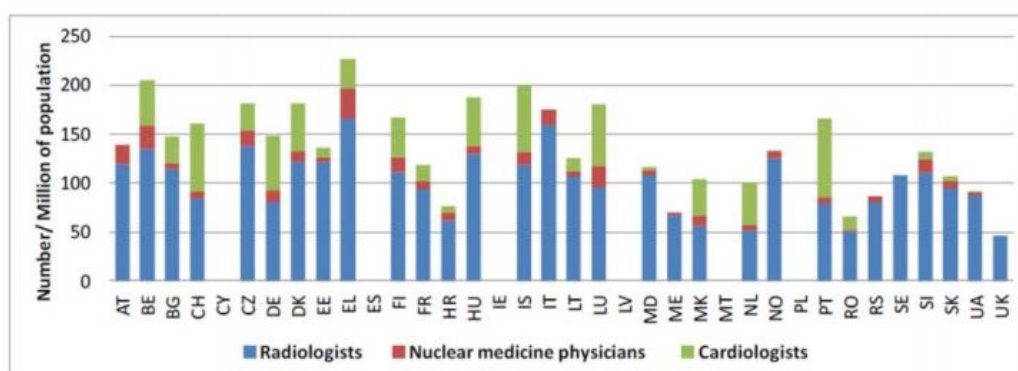


Figure 4.2. Numbers of specific health care professionals, per million of population. In case of no number, no information from the country has been available

Figure 63: Numbers of specific healthcare professionals

Plain radiography exams have remained quite stable in the last years in Europe, as opposed to a progressive growth of CT and MRI exams (Cf. previous §). Thus, the slow

²⁵⁴https://www.telemedicineclinic.com/wp-content/uploads/2016/11/Europes_looming_radiology_capacity_challenge-A_comparitive_study.pdf

growth of the radiologist workforce and the fast development of new and more complex technologies will become a major threat in the EU if no preventive actions are decided.

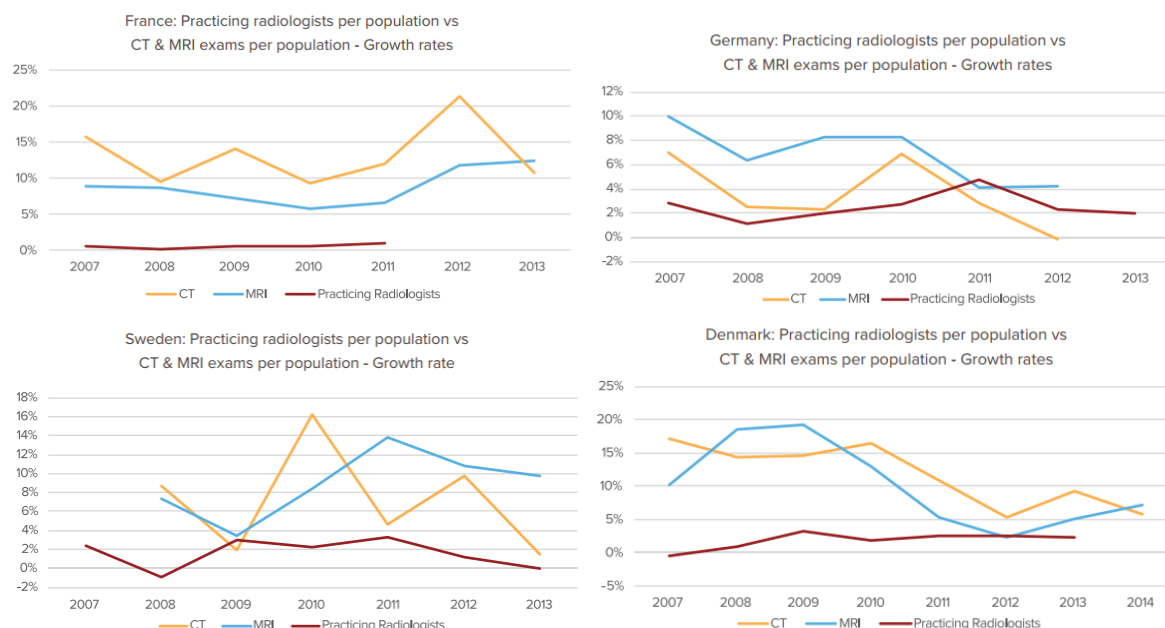


Figure 64: CT and MRI Growth Rate compared to Radiologists growth rate

The main issues in the EU are the following:

1. Lack of current available workforce (*in the UK 4370 FTE Radiologists were needed to satisfy the demand, only 2550 FTE were available, i.e. 60%*), leading to overtime hours or to image interpretation by non-radiologist specialists (*in Germany Orthopaedics interpreting image themselves*)
2. Growth rates of CT and MRI in EU Countries have almost continuously exceeded growth rates of practicing radiologists, thus widening the existing gap;
3. Progressive Ageing of Radiologist Workforce (*in France only 35% of the current workforce will be in activity in 2025*);
4. Geographical unequal distribution inside a country region (teleradiology can be a solution for facing this threat)

Europe is currently experiencing a complex demographic transformation which is increasing pressure on healthcare resources across the continent. Specifically, in the field of radiology there is a widening capacity gap driven by a steady increase in demand for cross-sectional imaging (CT and MRI) and a stagnating number of trained radiologists available to report these images. This is resulting in a significantly increasing workload for consultant radiologists and is a manifestation of an unparalleled capacity challenge in radiology.

European governments and institutions will have to address this as a matter of urgency. The challenge is significant and is manifested differently across European countries.

A.4.2. Teleradiology: a potential solution for staff shortage

A.4.2.1. Technological latest improvements

Teleradiology allows the physician in direct contact with the patient to have the advice of a radiologist located at a distance from the radiological examination site. In addition to this immediate benefit for the patient, teleradiology has the other advantage of promoting the exchange of knowledge and know-how between radiologist doctors who use it. The basic teleradiology tool is constituted, for tele-expertise or second opinion requests, of an independent computer unit devoted to this use, comprising a microcomputer adapted for handling radiological images, and connected to a communication network to carry out tele-transmission.

Today the Picture Archiving and Communication System (PACS) is widely used. It allows one to store, retrieve and display diagnostic images in a networked environment thanks to archiving functions. It allows network communication of images and thus remote or local network processing with computers with high-definition monitors for the visualization of radiological examinations. This system allows more efficient workflows, faster medical care delivery and potential costs savings.

The ESR (European Society of Radiology) launched two specific surveys in 2016 intended to gather the current state of adoption and implementation of teleradiology in clinical practice. A special focus on differentiating between insourcing teleradiology services among partners of the same organisation and outsourcing to external services was an essential part of the design of these surveys. The first survey was addressed to 44 national societies of different countries in Europe, while the second survey was intended for all practicing radiology ESR members.

The main conclusions²⁵⁵ of the Survey performed among national radiology societies (28 respondents among the 44 National Radiology Agencies in Europe) are:

Comparison of insourcing and outsourcing (key issues)		
	Insourcing	Outsourcing
1. Used?	74%	70.8%
2. Less than 5% of reports	56%	41.7%
3. Up to 25% of reports	32%	20.8%
4. Used as Part of daytime service	44%	41.7%
5. Nighthawk	52%	50%
6. Positive effect on service?	60%	16.7%
7. Not had a positive effect	12%	33.3%

Table 28 : Teleradiology survey results

The survey revealed that insourcing and outsourcing are used in many of the National Societies' countries and their use is relatively evenly balanced, insourcing being used slightly more frequently than outsourcing. However, when it comes to the positive impact on the service, it is perceived that insourcing²⁵⁶ mainly has a positive impact (60 %), whereas for outsourcing²⁵⁷ only 16.7 % perceived the impact to be positive. In 70.8 % of cases, the professional organisation stated that they did not in general support

²⁵⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4956619/>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579992/>

²⁵⁶ Insourcing – transfer of images between sites to enable the radiologist to work offsite or report images from remote locations, but employment arrangements are unaffected and radiologists are paid by one of the institutions

²⁵⁷ Outsourcing - Worklists are outsourced to teleradiology companies, which employ radiologists (see more detailed definition in the ESR white Paper on teleradiology)

outsourcing. Despite positive effects on workload and quicker turnaround times, outsourcing in particular is associated with significant concerns such as quality, legal issues, and reducing the clinical role of radiologists.

According to the survey result analysis it is clearly apparent that teleradiology is currently being used for a wide spectrum of purposes in Europe. The most common usage is in-house (intra-organisational or intra-institutional) distribution of imaging studies, as a tool for efficient workload sharing between the different locations of the same organisation (71 %). The second most popular application is on-call (preliminary) emergency readings from home (44 %). A relatively small portion (10 %) of the total number of participants is outsourcing images externally (transmission of images outside the organisation) to obtain second/expert opinions and to cover readings beyond office-time.

A.4.2.2. Teleradiology limitations and conditions for development

Despite a wide variety of teleradiology applications exist in Europe, the implementation mainly occurs in countries with a high concentration of networked PACS (Picture archiving and communication system), thus limiting its practical spread. Language remains an unsolved issue and a limiting factor for further deployment of services.

Regarding cross-border services, there is a great demand for a focused pan-European legislation, an adapted price regulation and a quality assurance framework. In summary, the ESR would foster a future EU legislation²⁵⁸ to provide the following:

1. Definition of teleradiology as a medical act in its own right.
2. Establishment of EU-wide accreditation criteria for teleradiology providers.
3. Emphasis on the importance of delivery of high-quality health care.
4. Application of international quality standards including monitoring of service providers.
5. Regulation of teleradiology as a responsibility of the member state where the patient undergoes the imaging procedure.
6. Full information of patients and informed consent about usage of teleradiology.

Teleradiology would also have to satisfy EU directives, such as Euratom BSS Directive that include very specific requirements for radiologists (clinical responsibility of radiologist, prior justification of a procedure) that could be challenging to set up.

²⁵⁸ http://www.myesr.org/sites/default/files/ESR%20teleradiology%20white%20paper_2014_art_10.1007_s13244-013-0307-z.pdf

A5. External Radiation Therapy

A.5.1. Foreword

In external beam radiation therapy ionizing radiation is typically generated in electron linear accelerators (linacs) or cyclotrons, resp. synchrotrons. The latter are in use for particle beam therapy. The patient is irradiated from outside typically from various angles. The main aim of this local treatment is to destroy cancer cells while sparing organs at risk and normal tissue as much as possible. For this the localisation of the tumour's extension is vital. Clear definition of the gross tumour volume (GTV) and clinical tumour volume (CTV), including sub-clinical disease spread is necessary. When considering uncertainties in treatment planning and dose delivering the planning target volume (PTV) is defined. To this end, external radiotherapy benefits from steady advances in medical imaging, equipment and computer science. In addition, the integration of drugs (chemotherapy, targeted therapy and immunotherapy) is of high value for external beam therapy. Many tumours are actually treated by a combination of radiation and drugs and the outcome in terms of tumour control and side effects largely depend on this association.

During the last two decades, radiotherapy has undergone major technological changes, with the appearance of "high" and "very high precision" techniques which make it possible to optimize the dose received over the entire tumour volume by optimally protecting healthy tissue. But it makes no sense to improve the accuracy of the beam if it is not possible to visualize or follow the target precisely. It is on these two sides (imaging and targeting) that technologies have evolved. A new technology does not necessarily replace the old one but can be associated with it, complement it and, moreover, has use for a different field.

Through time, the main improvements occurred on the beam shape (intensity modulated beam, dose distribution in 3D...) and on the imaging (prior and during the treatment session).

A novel very promising technique is entering the field, the MRI-linac. With this machine real-time verification and quick plan adoption to patient's anatomy is possible. This will lead to a more accurate treatment, thus better sparing of organs at risk and possibility of dose escalation. So far two companies (ViewRay and Elekta) offer MR-based treatment devices.

Brief Technology overview of Radiation Therapy Technologies

Conventional external beam radiation therapy consists of a single beam of radiation delivered to the patient from several directions. The first step is the CT simulation, performed to carefully plan the radiation treatment: determine the type of treatment field, energy source, and angles of the radiation beam.

Conformal radiation therapy 3D (3DCRT) makes it possible to correspond as precisely as possible (to conform) the volume on which the rays will be directed to the volume of the tumour. It uses 3D images of the tumour and bordering organs obtained by scanning, sometimes associated with other imaging examinations (MRI, PET, etc.).

Intensity-modulated radiation therapy (IMRT) relies on the voluntary and controlled variation of the dose within the beam itself. Thanks to dynamic collimation systems, it is now possible to rapidly vary the shape of the irradiated region during the treatment, according to a pre-defined schedule.

Volumetric arc therapy (VMAT) is an advanced form of IMRT that delivers radiation by rotating the gantry of a linac through one or more arcs with the radiation continuously on. As it does so, a number of parameters can be varied, including the multileaf collimator orientation and aperture shape, fluence-output rate and gantry rotation speed.

Image-guided radiation therapy (IGRT) allows to control the correct position of the tumour target under the treatment device and not just the patient. It is justified by the anatomical variations occurring during irradiation, which means that the dose delivered does not correspond to the planned dose, thus exposing the tumour to a risk of "under-dosing" (and therefore of recurrence) and the bordering organs to overdosage (and therefore of toxicity).

Stereotactic radiosurgery (SRS) can direct radiation beams to a very specific region, often small targets in the brain. *Stereo* means 3-dimensional (3D) and *tactic* means exploring. In stereotactic radiotherapy, treatment planning is complex and requires computers and devices that emit high-energy radiation. Computed tomography (CT) or magnetic resonance imaging (MRI) is used to locate and map the exact area to be treated. This helps to ensure that the normal tissue surrounding the tumour is not exposed to radiation. Nowadays, SRS is as well given to body targets and not only to brain lesions. It can require in some cases implantation of fiducials to precisely locating the target by IGRT.

A.5.2. Situation in the EU

The proportion of cancer patients for whom radiotherapy is part or all of treatment is estimated at 50%²⁵⁹ and, as the number of cases is likely to increase, it is necessary that all countries may be equipped with the best technologies combining efficiency and dose reduction. A survey was carried out in 2014 in the study HERO – the ESTRO Health Economics in Radiation Oncology project – in order to determine the furniture of radiotherapy technologies in Europe. This study focused on the presence of advanced technologies such as IMRT or IGRT among radiotherapy installations (mega voltage – MV) and personnel resources in different European countries. As regards equipment, the observations are as follows:

"Information about equipment for IMRT and IGRT was available for 26 countries; a total of 1327 out of 1915 MV units in 26 countries with this information available were equipped for IMRT (69%). IGRT equipment was available in 930 of 1915 MV units (49%). In seven countries (Albania, Belarus, Bulgaria, Hungary, Ireland, Lithuania, Spain) less than half of the MV machines were equipped for delivering IMRT, and in 13 countries (Albania, Montenegro, Hungary, Bulgaria, Belarus, Spain, Lithuania, Switzerland, Czech Republic, Ireland, United Kingdom, Slovenia, Portugal) less than half of the MV units were equipped for IGRT²⁶⁰."

While these radiotherapy tools are effective in treating cancer, there are wide disparities between countries. In addition, the more effective tools and that reduce the dose received by healthy tissues are not equitably present in all countries, as can be seen from the following graph obtained from HERO data²⁶⁰.

On the one hand Denmark has 9.5 radiotherapy units per million inhabitants, 94% of which have IMRT (and 89% IGRT), and Bulgaria, on the other hand, we find only 1.8 units per Mhab, 15% of which with IMRT (and 8% of IGRT). Some countries as Spain and Ireland, however, with a relatively large number of equipment show some delays in the implementation of up-to-date technologies.

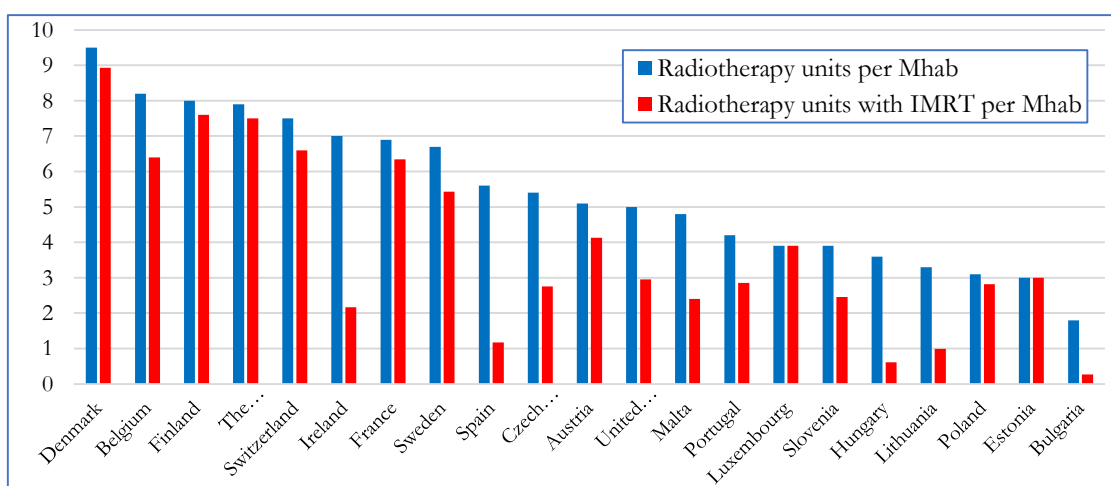


Figure 65 : Radiotherapy equipment in Europe

²⁵⁹ <https://www.ncbi.nlm.nih.gov/pubmed/16080176> and Radiotherapy equipment and departments in the European countries: Final results from the ESTRO-HERO survey. Radiotherapy and Oncology 112 (2014)

²⁶⁰ <http://www.sciencedirect.com/science/article/pii/S0167814014003594#t0005>

By analysing the number of patients treated by machines, it can be seen that the less equipped countries have to optimize their functioning by treating more than one thousand patients per year and per machine, whereas the best equipped countries record less than 300 patients per year per machine.

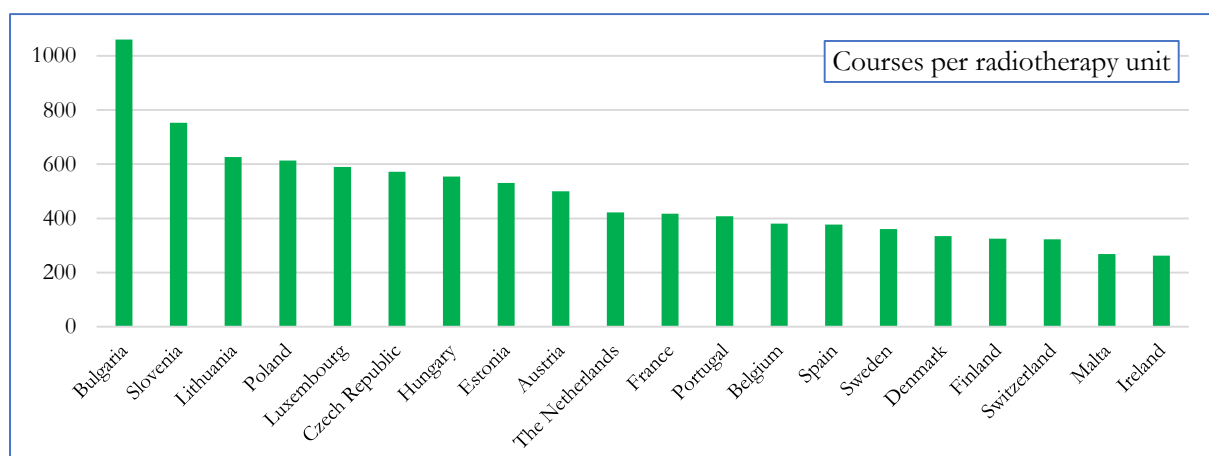


Figure 66 : Frequency of use of the radiotherapy equipment in Europe

The situation is much the same with respect to human resources. Indeed, with disparities according to profession, certain countries (Estonia, Hungary, Poland, Bulgaria) count less than 40 employees associated to the radiotherapy by million inhabitants while others (Denmark in head) are rich in it of more than 100 by million inhabitants. It should be noted that the personal functions might differ from country to country, e.g. in Denmark clinical oncologists take care of radiotherapy and medical oncology. Thus, data should be corrected if necessary to obtain comparable information.

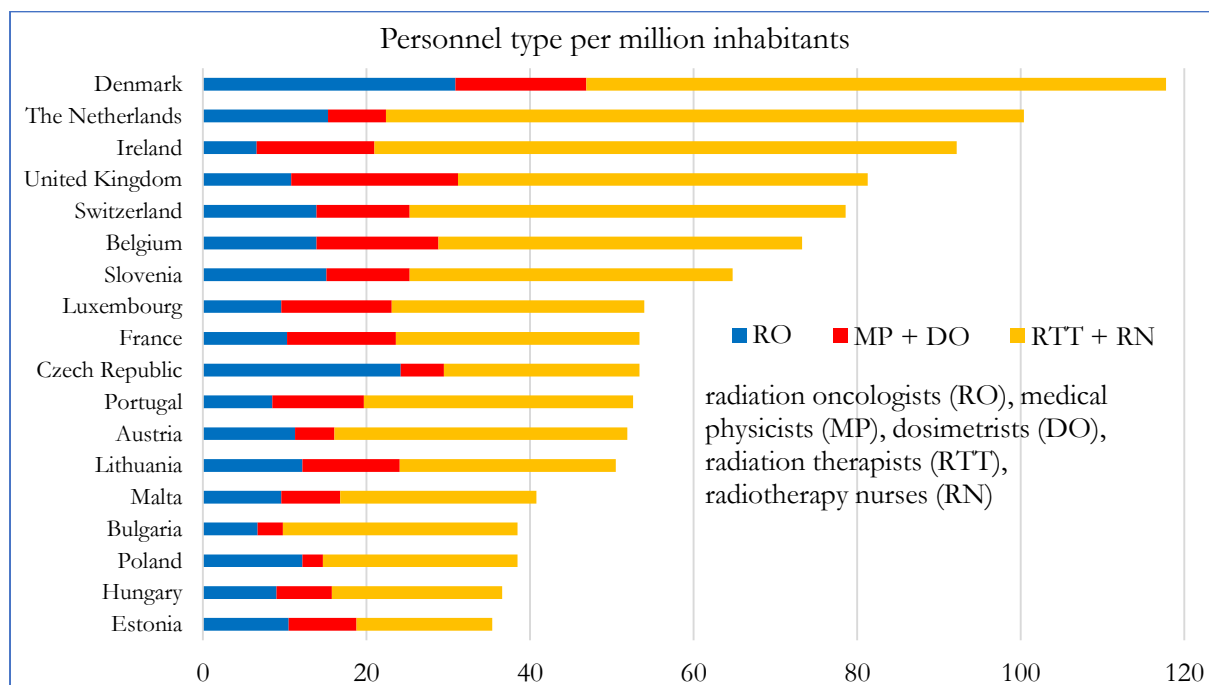


Figure 67 : Radiation therapy personnel in Europe

As a consequence, the staff, when they are fewer in number, must take on more patients and find themselves with a heavy workload (more than 900 patients to be managed per year per employee), while in others countries, staff can devote themselves to fewer patients (monthly 400 patients per year and per employee).

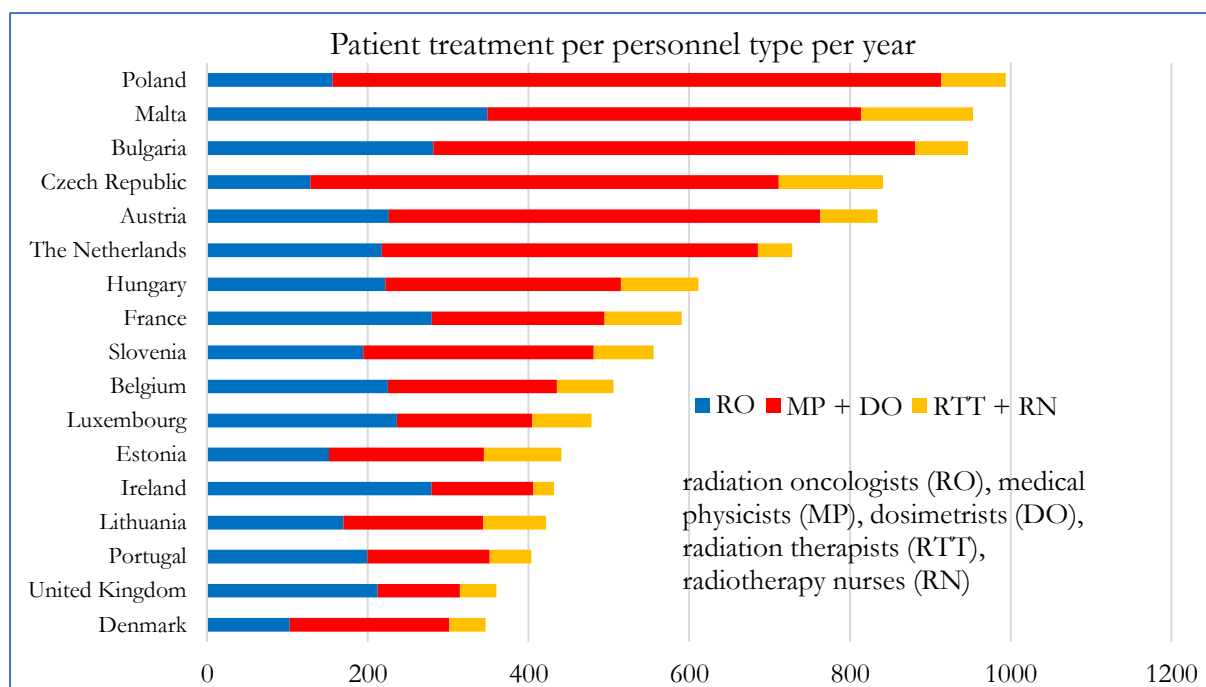


Figure 68 : Patients per staff type per year

A.5.3. The future of Radiation Therapy

A debate organized by ESTRO in 2016 (see §13.4.4) shows that the future of external radiotherapy versus other therapeutic means (biology, etc.) remains open and largely discussed among the experts and that R&D must be pursued. Brachytherapy is discussed in §13.5. Nuclear medicine therapy perspectives are detailed in chapter §12.1.4.4.

A.5.4. Future of X-Ray External radiation therapy

This article is taken from <http://medicalphysicsweb.org/cws/article/opinion/65059> and related to a debate at the recent (May 2016) ESTRO 35 conference in Turin, Italy. Pitting physicists against biologists, the ensuing discussion examined whether physics- or biology-based developments will better progress radiation therapies.

Physics or biology: where does radiotherapy's future lie?

What is the best way to maximize tumour control? Should we "crank up the volume" or "turn off the switches"? That was the intriguing theme of a debate at the recent ESTRO 35 conference in Turin, Italy. Pitting physicists against biologists, the ensuing discussion examined whether physics- or biology-based developments will better progress radiation therapies.

At the start of the debate, a show-of-hands vote revealed an audience preference for a biological approach. Could the speakers change the attendees' minds?

Reimagine the future

First to the podium, Bradly Wouters from the Princess Margaret Cancer Centre, argued the case for "turning off the switches" and exploiting knowledge of cell signalling, genetics and cell biology. He described three aspirations in radiation oncology-driven cancer treatment, the first being improvement of local tumour control. He pointed out that the progression of radiotherapy from 3D conformal to intensity-modulated, image-guided and adaptive treatments has certainly improved outcomes for patients, but that ongoing technical developments are now producing smaller gains.

While radiation is highly effective, the same can be said for cancer drugs, Wouters noted, citing the success of drugs developed to treat melanoma with the V600E BRAF mutation. "But even 'near perfect' drugs are limited by biology," he explained. When melanoma patients relapse after therapy, a physicist would say "give more drug, more conformal drug" – but the problem is not that the drug's not effective, the problem is the biological diversity in tumours. The way to achieve significant gain, Wouters proposed, lies in targeting that diversity, using knowledge gained from biopsies and imaging to tailor individual therapies and increase cure rates.

A second aspiration is treatment of systemic disease including oligometastases. The problem here, says Wouters, is that "you can only treat what you can see – and patients inevitably have cells that you can't see." Biological approaches such as immunotherapies may come into play here.

The third aspiration is reducing toxicity in cured patients. While normal tissue exposure will inevitably always be part of curative radiotherapy, there are new biological ways to approach this problem, via protection or regeneration of tissue. So why has biology not had a big impact in the field yet? "We're in the middle now, aiming for transformative change," said Wouters. "The question is, do we want more of the same, or to reimagine the future?"

Technology is key

"The past, the present and the future of radiation oncology is dominated by technological innovations," declared Jan-Jakob Sonke from the Netherlands Cancer Institute. Stating the case for keeping the focus on physics, Sonke noted that where we are now in the

clinic is mostly due to physics, following a century's worth of innovation; the only biology involved is fractionation.

One area ripe for improvement is global radiotherapy resources. Sonke pointed out that only 40% of patients worldwide currently have access to radiotherapy. The cost to increase global access to state-of-the-art radiotherapy is estimated at \$184 bn, but would provide a saving of some 26.9 m life-years and a net monetary benefit of \$278 bn. Such an undertaking would capitalize on existing technology innovations. It would require training of physicians and physicists but, Sonke noted, no radiation biologists would be required.

Sonke argued that upcoming technological innovations will further widen the therapeutic window. Adaptive replanning, for example, enables increased tumour dose by accounting for inter- and intra-fractional changes. Another recent advance is the introduction of dose painting. "It took a while to bring this to the clinic, but now trials are ongoing," he said. "We can deliver higher doses to regions of tumour, without extra organ-at-risk exposure."

Other developments include the proliferation of proton therapy, as well as the increasing use of carbon ion beams where, Sonke says, it is possible to exploit biology without using radiation biologists. Improvements in imaging systems will reduce the detectable lesion size, while the introduction of MR-guided radiotherapy will shrink treatment margins and lower toxicity.

Finally, Sonke highlighted the emergence of machine learning applications within medicine, with neural networks enabling analysis of large amounts of data, and radiomics furthering the understanding of tumour and normal tissue toxicity. Deep learning technology could identify the most radiosensitive patients and personalize their treatment accordingly. "There is some place for biology," Sonke concluded. "But not much."

Drug addition

Back to the biology, Alison Tree from the Institute of Cancer Research and The Royal Marsden took a look at the possibilities offered by adding drugs to radiation treatments. "Radiation has helped cure many cancers," she quoted. "However, its use in isolation has limitations that cannot be overcome by simple dose escalation."

For example, glioblastoma patients treated with dose-escalated radiotherapy exhibited a median overall survival of just 20 months. Patient data revealed that the tumour grows even in high-dose areas – it is simply not possible to deliver enough dose to achieve local control. Tree described a decade of studies examining the long-term impact of approaches including dose escalation, nodal irradiation, image-guidance and simultaneous integrated boost for treating prostate cancer. "As far as we can tell, not one of these made a single patient live a day longer," she stated.

Instead, drugs are needed that can shift the therapeutic curve to the left, and increase cure with less toxicity. Tree cited a recent paper on the integration of chemoradiation with molecularly targeted therapy. The authors proposed that exploiting biological differences between cancer and normal tissue might increase efficacy while maintaining tolerable toxicity. Promising approaches include combining chemoradiation with agents that modulate tumour-specific pathways, target the immune system or target angiogenesis.

This is not a new idea, said Tree, describing a study published in 2001 in which prostate cancer patients received radiotherapy with or without androgen suppression. Adding androgen suppression improved the 10-year overall survival from 40% to 58%. "When did you see improvements like that in radiotherapy?" she asked. Promising results have also been reported for combining immunotherapy (for example, drugs that turn off the T cell inhibitor PD-L1) with radiation.

"We have already 'cranked up the volume', and spent half a century perfecting our techniques," Tree concluded. "But if you only have a hammer, you see all problems as a nail – we now need to break out the power tools and benefit patients."

Too complex a system

The last speaker, Andre Dekker from MAASTRO, aimed to persuade the audience that "we need less biology". Tumours and normal tissues are complex systems, he explained, and we don't yet understand complex systems. As such, it is extremely hard and sometimes impossible to predict what will happen. Instead, suggested Dekker, we need to stick to the basic science. "It is too early to start switching, you'll break things," he said.

Dekker took a look at the current success of drug development in biology, noting that only 15% of drugs make it from phase I trials to clinical approval. And in oncology, only 7% of drugs are approved, because of efficacy and safety issues. He also emphasized the inconsistency associated with biology. For example, only six of 53 "landmark" cancer studies by the biopharmaceutical company AMGen were reproduced, while published target-validation results from pharmaceutical company Bayer were reproduced in only 14 of 67 of projects. Dekker cited a 2015 study that estimated the cost of irreproducible biology research at \$28 bn per year in the US. "And even if you get a drug that works, it's going to cost you," he added, quoting the price for one year of life at \$207 000 in 2013. "As Jan-Jakob said, physics just needs \$184 bn to save 27m life-years, that's \$7000 per life-year, two orders of magnitude cheaper than biology."

End game

The debate was rounded off with challenges posed from the biologists to the physicists and vice versa. The physicists were asked whether they have now reached the pinnacle of their field, with no way to substantially improve outcomes. Sonke disagreed, citing fractionation, machine learning and individualization of treatment as ways forward. "And our toolset is sufficient to achieve this," Dekker added. Dekker then challenged the biologists to convince him that in the next 5–10 years biology will be quantitative not qualitative and move towards having effects in the full population. "We don't need to fully understand biological systems to intervene and have an effect," replied Wouters, citing the example of the breast cancer drug Herceptin. "You don't have to understand everything about it to make patients' lives better," Tree concurred.

The final show-of-hands vote

The session finished with a second show-of-hands vote. Again the majority of the audience picked biology as the way forward, but the result was a close call, with an increased number thinking physics to be better option. As such, the session chairs declared both sides to be winners.

Tami Freeman is editor of medicalphysicsweb.

A6. Brachytherapy

A.6.1. Foreword

Brachytherapy can treat malignant tumours, especially the breast, genital organs (prostate and gynaecological tract), the skin, or the head and neck region, alone or in addition to another treatment. Consisting of placing radioactive isotopes (sources) within or near a tumour, it has the benefit of ultra-high radiation dose delivery to the tissue adjacent to the radioisotope but a rapid fall-off of radiation dose as distance from the source increases, so organs at risk can be spared. Brachytherapy made important improvements in the last years²⁶¹ like the integration of 3D imaging, real-time implants, in-vivo dosimetry, and advanced dose calculation algorithms. This made brachytherapy for many tumour sites (e.g. prostate, gynaecological tumours, breast) a very attractive treatment option with excellent patient outcome and low toxicity. Not to forget the relative low costs of brachytherapy. The availability for brachytherapy nuclides (e.g. I-125, Ir-192, Co-60, Rh-106) must be secured in Europe.

Low-dose-rate (LDR) brachytherapy

LDR brachytherapy delivers dose rates of 0.4 to 2 Gray (Gy) per hour. The sources of Iodine-125 are intended for applications inside the tissues, typically the prostate. The sources the so-called seeds, typical between 30 and 80, are implanted under ultrasound guidance and remain permanently into the prostate gland.

Pulsed-dose-rate (PDR) brachytherapy

During pulse rate brachytherapy, the radioactive source of iridium-192 is by an afterloading machine projected for a few minutes, every hour, but other time schemes exist. The source advances inside the cables, not continuously, but in steps of 2.5 to 5 millimetres. The duration of stopping between each step defines a given quantity of radiation, thus making it possible to adapt the irradiation to the shape of the tumour as best as possible. PDR brachytherapy is a complex but relative mild treatment form.

High-dose-rate (HDR) brachytherapy

This brachytherapy method uses a radioactive source of iridium-192 that has a much higher activity than that used for pulse or low-dose rate brachytherapy (up to 370 GBq) delivering dose rates greater than 12 Gy /h. Moreover, the source is delivered for a very short time (a few minutes). Often, HDR brachytherapy can be performed as in ambulatory setting. The patient goes to the hospital for the session (about 30 minutes) and then returns home provided the applicator does not need surgical placement. The number of sessions varies from 1 to ≥ 6 , divided into one to several times a week. HDR brachytherapy is the most common and universal form of brachytherapy.

²⁶¹ See e.g. Haie-Meder C, Siebert FA, Pötter R (2011) Image guided, adaptive, accelerated, high dose brachytherapy as model for advanced small volume radiotherapy. *Radiother Oncol* 100 (2011) 333–343

A.6.2. Situation in the EU

The comparison of 2013 and 2017 version of the DIRAC database²⁶² gives a recent picture of Brachytherapy use in the EU and evolution trends:

	2013 ²⁶³	2017
Nb of Brachytherapy systems	945	837
HDR Sources	546	476
LDR Sources	328	181
MDR Sources	31	19
PDR Sources	40	46
Brachytherapy equipped centres	52%	50.7%
Centres with Remote after-loading	562	643
Centres with Manual after-loading	125	133

Table 29 : DIRAC stats on brachytherapy systems

837 brachytherapy systems were identified; these included 643 remote after-loading machines and 133 manual brachytherapy systems. 476 machines used HDR sources, 181 used LDR, 19 used medium dose rate, and 46 used PDR. Overall, 593 centres in Europe had brachytherapy facilities, representing about 50% of all radiotherapy centres. For individual countries, the percentage of centres with brachytherapy systems varied from less than 40% of centres in France, Italy, and Spain, to 60% or more in northern, eastern, and south-eastern European countries.

A.6.3. Therapy cost

Another important aspect of brachytherapy is the cost of therapy. Brachytherapy equipment is the least expensive of all available radiation therapy equipment and because treatment is performed in one or two days the total cost of treatment is limited particularly when compared to surgery or a prolonged course of external beam radiotherapy. The cost of installation of a brachytherapy unit is in the order of €400-600K, whereas for an IMRT linear accelerator is €2-3M and a proton centre €100-300M. Labour costs are another expense that determines the overall cost of treatment.

As an example, published data from the United States, facing the same issues as in Europe, shows the large differences in cost of prostate cancer treatment estimated to be \$2395, \$5467, and \$23,665 for LDR, HDR and IMRT, respectively²⁶⁴.

²⁶² Since 1959, the IAEA has maintained a register of radiotherapy hospitals and clinical institutions having radionuclide and high-energy teletherapy machines: DIRAC database. It includes data not only on teletherapy machines, but also on sources and devices used in brachytherapy, and on equipment for dosimetry, patient dose calculation and quality assurance. Staff strength at the installations (radiation oncologists, medical physicists, technicians, etc.) is included as well.

²⁶³ Radiotherapy capacity in European countries: an analysis of the Directory of Radiotherapy Centres (DIRAC) database Eduardo Rosenblatt, Joanna Izewska, YavuzAnacak, YaroslavPynda, Pierre Scalliet, Mathieu Boniol, Philippe Autier

²⁶⁴ Shah C, Lanni TB, Jr., Ghilezan MI, Gustafson GS, Marvin KS, Ye H, et al. Brachytherapy provides comparable outcomes and improved cost-effectiveness in the treatment of low/intermediate prostate cancer. Brachytherapy. 2012;11:441-5.

A7. Proton Therapy

A.7.1. Proton therapy principle

Particle therapy treatment techniques (also called *hadron therapy*) are based on Neutrons, Positive Ions and Protons utilization. Among those technologies, proton therapy has become the most promising technique in radiotherapy.

Despite first treatments being performed in the 50's, the major growth of proton therapy occurred at the beginning of the 21st century. Research activities on proton therapy have escalated in the last decade, scientific publications were multiplied by five between 2010 and 2016²⁶⁵.

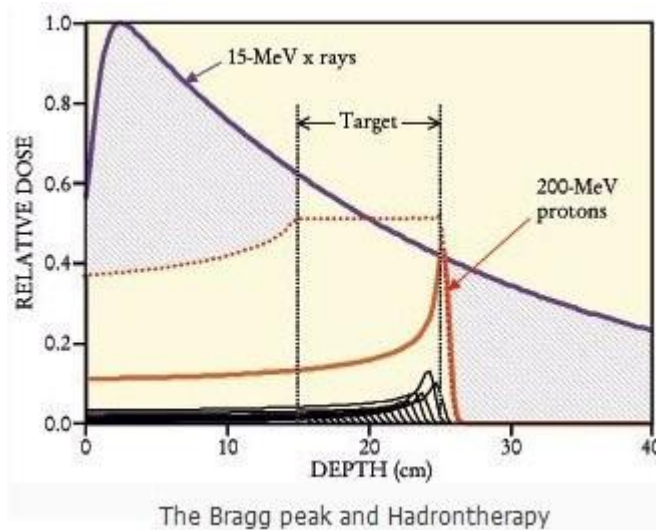


Figure 69: Comparison of depth dose distribution

Proton therapy efficiency is based on the physical principal of the Bragg peak: a fast-charged particle deposits a limited dose on its way but delivers is destructive power in very little distance (*as shown in the upper figure*). This minimizes the dose received by the patient's healthy tissues, before and after the area to be treated, while allowing to destroy the tumour with much efficiency. The depth of the peak depends on the energy and the mass of the particle and this allows for precise targeting of the tumour. This is the main advantage over the radiotherapy, using X or γ-rays (the most relevant being photon Intensity-Modulated Radiation Therapy - IMRT) which give a maximum dose near the surface and a continuously reducing dose with depth. Even though relatively few studies and trials have yet fully compared the side effects due to either technology.

The fixed-energy proton beam is distributed by the high energy beam transport line to the treatment rooms. Some of them are horizontal or vertical fixed beam stations for treatment or used for quality assurance, development and research activities. In other installations, the beam is guided along an isocentric gantry allowing irradiation from all directions.

For the treatment, a degrader or a modulator can be used to change the energy of the proton beam (in the case of a cyclotron).

²⁶⁵ Based on NCBI/PubMed publications on Proton therapy on the period 2010-2016



Figure 70: Courtesy Hakan Nyström - Layout of the Danish Center for Particle Therapy (cyclotron and three treatment rooms).

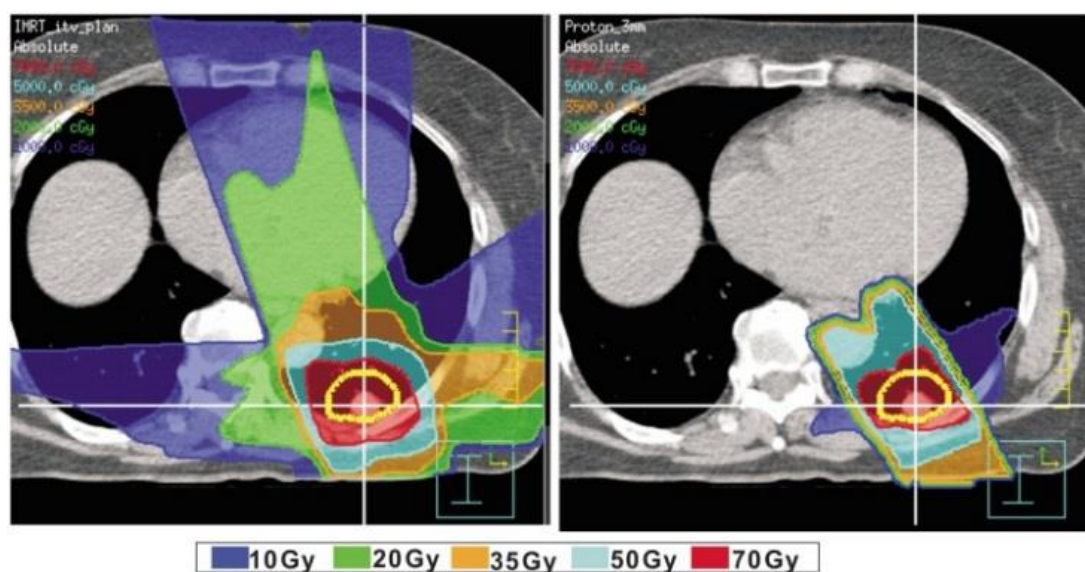


Figure 71: Comparison of photon intensity-modulated radiation therapy (IMRT) plan (left) and proton therapy plan (right). (Chang, 2011)

A.7.2. Some figures about proton therapy evolution and market

Despite its recent growth of interest, proton therapy is a rather old technology that was first introduced in Europe in Sweden in 1957 at the Uppsala University, a few years after Berkeley (USA) first patient treatments. During the last twenty years, 60 proton therapy centres opened throughout the world (*24 centres in the USA and 14 in Japan*) contributing to a major renewal of the technology. Between 2000 and 2010 roughly 2.5 treatment rooms (*Gantry or Fixed Beams*²⁶⁶) were opened in average each year. The substantial growth of proton therapy occurred in the period 2011-2017, with an average of 10 additional treatment rooms per year. This trend is expected to continue for a few years, at least until end of 2020²⁶⁷. In the short term, there is a large market to equip countries with proton therapy centres, thus competition between players is rather strong. In the European Union, proton therapy will soon be available in 13 member-states²⁶⁸.

This worldwide development boosted the proton therapy equipment market, which is expected to reach 1 billion USD in 2019²⁶⁹. Several companies are competing on this sector: main actors being IBA, Hitachi, Varian, Mitsubishi, SHI. Figure 71 indicates the breakdown of treatment rooms in the world at the end of 2016 (*including project under construction and signed contracts*). By the end of 2015, roughly 30 000 patients have been treated with proton therapy in Europe, since its introduction in 1957.

Proton therapy treatment costs differs from one country to another, in the USA, cost range is 32-50k\$₂₀₁₆²⁷⁰ for a prostate cancer treatment; whereas in Prague treatment would be charged 26k\$₂₀₁₄²⁷¹. Treatment costs depend of many parameters: equipment investment costs, hospital's staff size, national reimbursement structure, etc. Major cost gaps with others treatment procedures (radiotherapy, IMRT...) remain a major issue for protontherapy development.

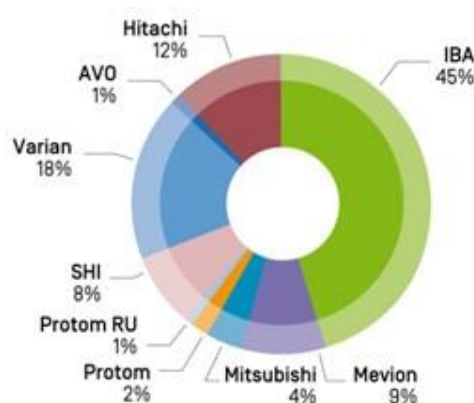


Figure 72: Installed base of Proton therapy treatment rooms in 2016 (including projects under construction)

²⁶⁶ The gantry is a large, cylindrical or conic shaped structure that houses the equipment used to actually give the protons to the patient. The gantry allows the beam to spin 360 degrees around the patient. Where a fixed-beam treatment room does not require the gantry because the beam does not move around the patient.

²⁶⁷ Projections for 2018-2020 period are based on Particle Therapy Co-Operative Group (PTCOG) data, considering projects under construction and those at a planning stage.

<https://www.ptcog.ch/index.php/facilities-under-construction>

²⁶⁸ See Appendix A - Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Poland, Slovak Republic, Spain, Sweden, United-Kingdom

²⁶⁹ <https://www.itnonline.com/article/proton-therapy-world-market-expected-reach-1-billion-2019>

²⁷⁰ <http://www.usmdpcc.com/news-proton-therapy-for-prostate-cancer.php> or <http://ascopubs.org/doi/full/10.1200/jop.2015.005694>

²⁷¹ <http://www.standard.co.uk/news/health/i-went-abroad-for-prostate-cancer-therapy-and-im-sending-the-nhs-my-17000-bill-9127633.html>

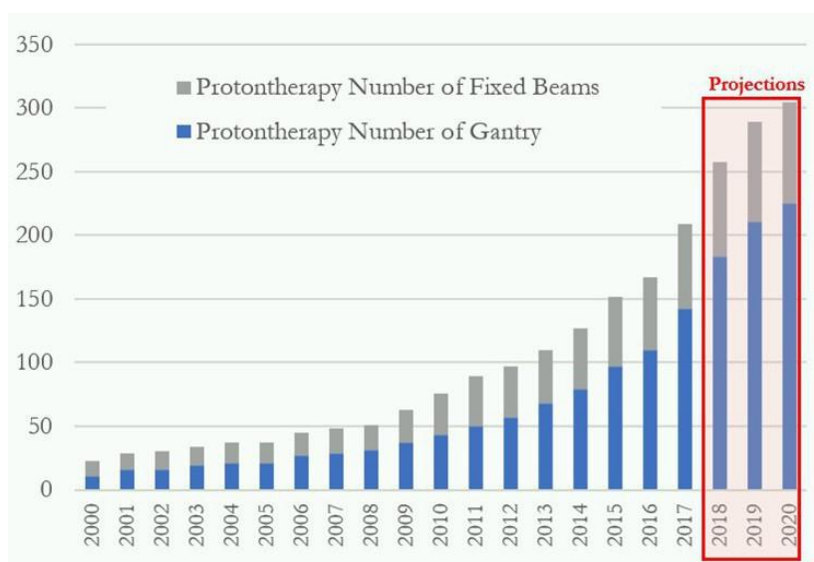


Figure 73: Proton therapy treatment rooms evolution between 2000 and 2020 (Worldwide)

Before discussing whether the future installed capacity is enough to cover European Union needs, it is essential to develop the major uncertainties linked to proton therapy treatment, respectively cost efficiency and low level of evidence of proton therapy added benefit as compared with others technologies.

A.7.3. The need for scientific evidence of the clinical benefits of Proton therapy

Despite its theoretical superiority to radiotherapy in terms of dose distribution for the healthy tissues and organs, proton therapy today suffers from a lack of wide evidences to confirm or infirm its clinical efficiency compared to radiotherapy modern techniques, several statements from National Health Societies are provided in Box n°1. For proton therapy, clinical research is still in phase II.

Box n°1 –Proton therapy lack of clinical evidence survey

Canada – AETMIS - La protonthérapie. Note informative préparée par Jean-Marie R. Lance. (2010)

« Les auteurs ont conclu que les données probantes actuelles étaient insuffisantes, puisque les études sur l'efficacité et l'innocuité de la protonthérapie n'incluaient que dans de très peu de cas un comparateur (autre technique de radiothérapie ou chirurgie, par exemple), ciblaient des populations hétérogènes et employaient des définitions variées de résultats et d'effets indésirables »

France – Proton therapy, indications and treatment capacity (June 2016)

"Il est important de préciser qu'une très grande majorité des documents analysés ont pointé le manque de données scientifiques et la faiblesse méthodologique des études existantes (aucun essai contrôlé randomisé de phase 3 comparant la protonthérapie aux techniques récentes de photonthérapie recensé dans les recommandations identifiées)"

Austria - Hadronentherapie: Protonen und Kohlenstoff-Ionen Eine Übersicht: Refundierungsstatus Evidenz und Forschungsstand (2013)

"The evidence basis for an added benefit is only very moderate. Since surrogate endpoints were primarily measured and no/hardly any prospectively comparative trial results with up-to-date photon therapy are available, there is no confirmed knowledge of whether the promise of theoretical advantages can be translated into patient-relevant advantages (longer survival, quality of life through fewer side effects). MedAustron is to be considered primarily as a scientific project for the execution of appropriate trials and to be funded accordingly. »

Proton therapy treatments' efficiency for very specialized pathologies such as eyes cancers or base of skull chordomas is unquestioned, but its preferential use for other forms of tumours has not been sufficiently assessed.

Tabel 6.1 Outcome of systematic review: effectiveness of proton therapy compared with conventional therapy, grouped according to tumour site (Lodge 2007).

tumour site	number of studies	number of patients	outcome
head and neck	2	62	no firm conclusions
prostate	3	1,751	protons similar to photons
eye	10	7,708	protons superior to photons
gastro-intestinal	5	369	no firm conclusions
lung (NSC)	3	156	no firm conclusions
CNS	10	839	protons similar to photons
base of skull chordomas	3	302	protons superior to photons
sarcoma's	1	47	no firm conclusions
pelvis	3	80	no firm conclusions

Table 30 : Proton therapy needs to prove its effectiveness

In the last few decades, very few Clinical Randomized Controlled Trials²⁷² (RCT) have been performed to support comparative analysis with state of the art radiotherapy (IMRT, VMAT, etc.). For this reason, several countries intend to develop their proton therapy capacity in order to perform clinical evaluations to study its interest compared to other technologies before large-scale deployment. More than 300 clinical trials are currently under implementation, with limited international clinical trials between Member States.

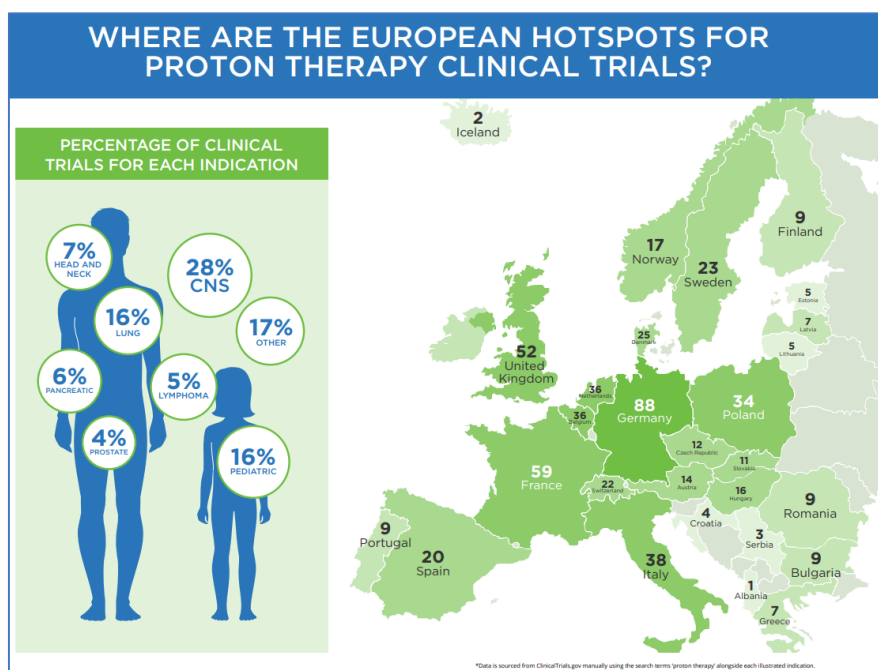


Figure 74: Proton therapy clinical trials under implementation as of November 2016

Nevertheless, a sole RCT does not necessarily appear as the optimal approach to perform those comparisons; some late radiation-induced complications have very long latent times, e.g. the development of cardiovascular complications generally takes at least 5 years, and the incidence in particular continues to increase up to twenty years after initial

²⁷² A randomized controlled trial is a type of scientific medical experiment which aims to reduce bias when testing a new treatment. The people participating in the trial are randomly allocated to either the group receiving the treatment under investigation or to a group receiving standard treatment (or placebo treatment) as the control. Randomization minimizes selection bias and the different comparison groups allow the researchers to determine any effects of the treatment when compared with the no treatment (control) group, while other variables are kept constant.

treatment. In such cases, an RCT would take at least 15 to 20 years to come up with useful information regarding the primary endpoint. For these reasons, it may be essential to efficiently orientate patients towards a specific technique using a different approach.

Internal predictive dosimetry and fast computing ability enable medical community to use innovative predicting approaches such as “Normal Tissue Complication Probability – NTCP”, that would enable patients to receive the most adequate treatment for their pathologies.

Normal Tissue Complication Probability Approach

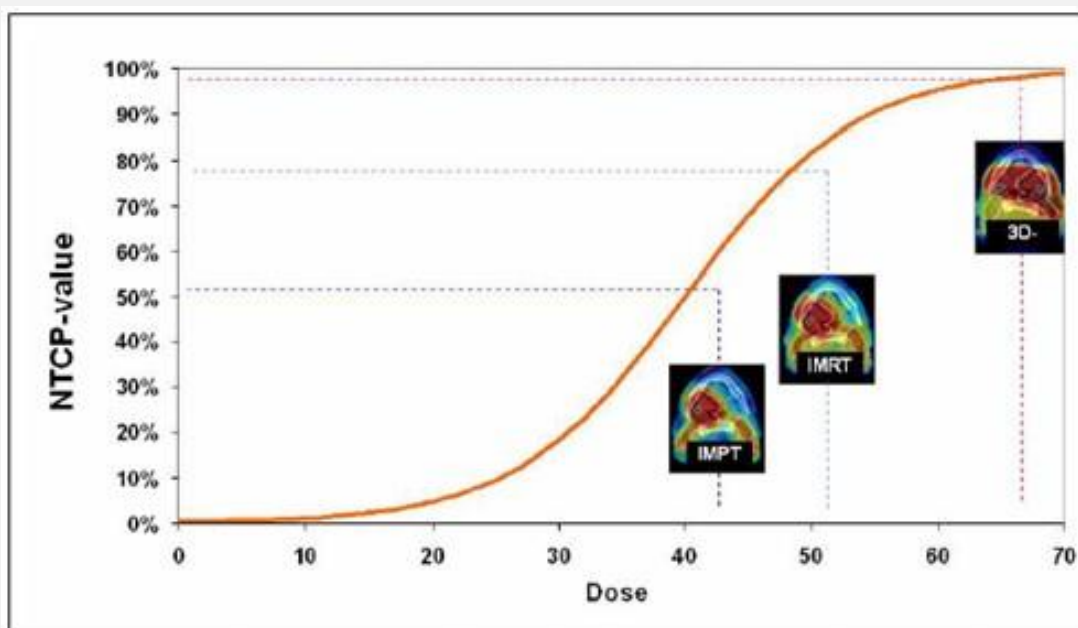


Figure 5.3 Translation of differences in dose distribution into clinical benefit in terms of the probability of complications. The reduction of the dose in the parotid glands obtained with IMRT (photons) compared to 3D-CRT photons results in a reduction of the NTCP-value from 97% to 77%. Further NTCP-reduction (to 50%) can be achieved with the use of proton IMPT.

Figure 75: Translation of differences in dose distribution into clinical benefit in terms of the probability of complications

NTCP consists in a three-step approach:

1. Normal Tissue Complication Probability Assessment.
The basic principle in the development of new radiation delivery techniques is the existence of validated relationships between dose distributions in critical organs and the probability of radiation-induced side effects (i.e. Normal Tissue Complication Probability - NTCP). In general, the NTCP-value will increase with increasing dose and increasing volume that receives a certain dose.
2. Evaluation of the theoretical dose received for different techniques (IMRT, Proton therapy...)
3. Model-based studies.
The final step will be to determine to what extent the optimised physical dose distributions will translate into a clinically relevant beneficial effect, using the combination of data from existing NTCP-models and treatment-planning comparative studies.

Such a method could permit to minimize RCT to areas where a real uncertainty exists between proton therapy and radiotherapy.

In order to support these studies (RCT and NTCP), international European cooperation²⁷³ should be conducted to improve the exhaustiveness of proton therapy treatment justification. European Commission could promote & support such inter-country initiatives. Sharing information on radiation-induced complications between EU-countries could benefit the Medical Community, along with international patient-controlled trial selection.

A.7.4. Proton therapy Business Model & Cost-effectiveness

Proton therapy development was based on a paradox: although the technology is recognized as a preferred option for treating children and some specific cancers (eye, base of skull chordomas), these cases are not prevalent enough to fill the necessary spots in centres. Thus, in some countries (USA mainly) proton therapy centres have aggressively advertised their services for prostate cancer and other more common forms of cancer to maximize their revenue potential. For years, the protontherapy business model was based on prostate cancer.

In the USA, the situation is now different, reimbursements for prostate cancer proton therapy have decreased (*Blue Shield of California, Aetna, and Cigna Corp are no longer covering proton therapy as a treatment option for localized prostate cancer*²⁷⁴, and *Medicare reduced reimbursement up to 32k\$*), thus debt-financed proton therapy centres will face steep challenges to remain financially viable. Paradoxically, reduced reimbursement for common cancer will require proton therapy centres to treat more cases for which it has demonstrated superior outcomes. Relative losses will be highest for those facilities focused primarily on treating noncomplex cases²⁷⁵. In 2014, The Indiana University Proton Therapy Center closed its operations (*first shutdown of a proton-beam therapy centre in the United States*). The shutdown was attributed to the centre's untenable financial losses. Insurers are beginning to push back on their coverage of proton-beam therapy until sufficient data prove its efficacy over less expensive modalities.

Treating "common forms of cancer" with proton therapy does not necessarily appear cost-efficient. A very limited number of publications evaluate the cost-efficiency of proton therapy for "non-standard applications". The lack of data risk is clearly identified by Medical Community. The few studies based on Cost and QALY indicator (*Quality Adjusted Life Years*²⁷⁶) shows that proton therapy is efficient for paediatrics cancer treatments²⁷⁷, brings no particular benefit for prostate cancer²⁷⁸ (*toxicity is equivalent with higher price*), and is similar to other treatments²⁷⁹ for intraocular melanoma.

Aside from cost-efficiency, proton therapy installations costs must be detailed. Investment costs for proton therapy centres decreased through the years, a standard centre with a cyclotron & 3 treatment rooms costs in the range of 100M€ with annual

²⁷³ Appendix C deals with previous European Initiatives on Proton therapy

²⁷⁴ <http://www.ascopost.com/issues/august-10-2015/is-proton-beam-therapy-facing-a-difficult-future/>

²⁷⁵ <https://www.ncbi.nlm.nih.gov/pubmed/23265572>

²⁷⁶ The QALY is a measure of the value of health outcomes.

²⁷⁷ Cost Effectiveness of Proton versus Photon Radiation Therapy with Respect to the Risk of Growth Hormone Deficiency in Children. <https://www.ncbi.nlm.nih.gov/pubmed/25641407> (2015)

²⁷⁸ Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity <https://www.ncbi.nlm.nih.gov/pubmed/23243199> (2013)

²⁷⁹ Cost-effectiveness of proton beam therapy for intraocular melanoma. <https://www.ncbi.nlm.nih.gov/pubmed/25993284> (2015)

costs in the range of 10-25M€²⁸⁰, whereas a single treatment room installation costs 30-40M€²⁸¹ (Cyclotron cost for such installation being in the range of 10M€).

Proton therapy treatment cost is much complex to evaluate, as it is strongly linked to centre & country specificities (*manpower cost, daily operating time, manpower volume, type and complexity of the pathology treated, indirect costs, etc.*), but recent comparative analysis showed that proton therapy remain more expensive than other technologies²⁸².

Table 8.1 Lifetime costs and quality-adjusted life expectancy, by treatment type.		
Treatment	Cost	QALY's
Brachytherapy	\$29.575	13,90
IMRT	\$41.591	13,81
Proton therapy	\$72.789	13,70

Figure 76: Lifetime costs and quality-adjusted life expectancy by treatment type - Proton Radiotherapy, Horizon Scanning Group – Health Council of the Netherlands (2009)

Proton therapy is expected to pursue its technological development in the next decade, through for example, the development of volumetric image guidance. Potential savings could also come from gantry replacement to compact beam delivery equipment. As of today, Proton therapy treatment cost is twice the cost of IMRT and a full treatment in EU is around 25k€.

A.7.5. Estimate of proton therapy future demand – based on Netherlands Case Study

Prior to the decision to build proton therapy centres in Netherlands, the Health Council of the Netherlands performed in 2009²⁸³ an assessment of its potential demand. When considering standard indications (intra-ocular melanoma, base of skull/paraspinal tumours and paediatric tumours), 252 patients could have been treated with proton therapy in Netherlands. It is equivalent to 15 patients per million of inhabitants. Other European countries also established targets for standard protontherapy treatments, 4.3 standard indications per Mhabitants in Belgium, 9 in Sweden, 16.6 in Italy, and 8 per Mhab in United Kingdom²⁸⁴. In order to satisfy these objectives, 75 treatment lines (gantry of fixed beams) could be necessary in EU in order to treat all the standards indications with proton therapy²⁸⁵. There will be 67 proton therapy lines in 2018²⁸⁶ that should satisfy demand. Proton therapy further development would imply to extend its scope to additional indications. For instance, the Health Council of the Netherlands performed evaluations of future potential use of the technology.

²⁸⁰ Protonthérapie, indications et capacité de traitement, Institut national du cancer (2016)

²⁸¹ Beaumont Proton therapy Center cost: 40M\$₂₀₁₅ <https://www.beaumont.org/health-wellness/press-releases/beaumont-health-first-in-michigan-to-treat-cancer-patient-with-protons>

²⁸² Cost-comparativeness of proton versus photon therapy
<http://cco.amegroups.com/article/view/11097/11904>

²⁸³ Proton Radiotherapy, Horizon Scanning Group – Health Council of the Netherlands (2009)

²⁸⁴ « Protonthérapie, indications et capacité de traitement/juin 2016 » (Institut national du cancer)

²⁸⁵ Average centre patient treatment was assessed based on PTCOG data, a centre is considered able to treat 110 patients per year. This hypothesis can be considered very conservative, where new US proton therapy centre intends to treat 300-500 patients per year. <http://www.candqnews.com/news/40-million-beaumont-proton-therapy-center-celebrates-first-patient-102681>

²⁸⁶ 23 are actually in construction in UK (10), Netherlands (5), Denmark (4), Belgium (2), Slovakia (1) and France (1).

Table 7.1 Estimated total number of patients eligible for proton radiotherapy in the Netherlands.

Indication	Total number of patients with cancer in NL 2005 ^a	Number of patients treated with RT ^b	Estimated number of patients eligible for proton radiotherapy ^c
Standard indications	550	299	252
Potential Indications	21,061	14,471	1,215
Model-based indications	52,795	34,697	4,824
Reduction of secondary tumours	15,277	11,171	807
Total			7,098

- a Total annual number of patients with specific type of cancer in the Netherlands, based on Dutch Cancer Registry 2005.
b Estimated number of patients with specific type of cancer to be treated with radiotherapy, based on CCORE report and adapted in NVRO report.
c Estimated number of patients with specific type of cancer eligible for proton radiotherapy based available *in-silico* studies and expert opinion.

Figure 77: Estimated total number of patients eligible for proton radiotherapy in the Netherlands

Based on these Dutch evaluation statistics, on the European Union Scale, the number of European patients eligible for proton therapy (taking into account potential indications, model-based indications, and reduction of secondary tumours) would be:

Indication	Patients with cancer in EU	Patients treated with RT	Patients eligible for proton therapy	
			<i>in % of RT</i>	<i>in Nb</i>
Standard indications	17 152	9 325	0,6%	9 144
Potential indications	656 809	451 293	3,0%	45 719
Model-based indications	1 646 465	1 063 349	12,1%	184 400
Reduction of secondary tumours	476 429	348 379	2,0%	30 479
Total	/	/	17.7%	269 742

Figure 78: Estimated total number of patients eligible for proton therapy in EU-28

In these conditions, the proportion of patients treated with radiotherapy who could benefit of proton therapy could be up to 17.7 %. Based on such figures, IBA evaluated to 2 502 the number of PT rooms needed worldwide which means could increase the demand up to 950 treatment rooms in European Union²⁸⁷ on a long-term basis, when largely increasing the number of indications to be treated with Proton Therapy. This is a very optimistic scenario, implying deep changes in the way to treat cancers.

The results of the future studies on proton therapy effectiveness towards other technologies would enable countries to take decisions on the use of proton therapy, for additional indications.

²⁸⁷ IBA considers that 284 patients can be supported by a room per year, it's consistent with Nice and Berlin proton therapy centres, where only ocular tumour are treated with one fixed beam room, an average (between 2008 and 2015) of 240 patients benefited from the treatment.

A8. Carbon-ion therapy

Proton and carbon ion beams provide superior dose distribution compared with the most advanced photon technology (see figure on the upper right). A Bragg peak is typical for proton and carbon ion beams, but only in carbon ions a little tail from nuclear fragmentation appears behind the Bragg peak. Several Bragg Peaks are summed up to the Spread-out-Bragg peak (SOBP) (see figure on the bottom right). Despite this, differences exist in terms of physical characteristics of the energy transfer. By using carbon ions, a smaller-dose penumbra (width of the dose band lateral to the field edge where dose decrease from 80% to 20%) can be reached compared with protons (see figure attached), thus allowing to increase even more the dose distribution. In general, it can be stated that the higher the mass of charged particles, the higher the rate of energy losses while penetrating tissue. Thus, the linear energy transfer (LET) is higher for carbon ions compared with protons. Clinical proton beams are low LET with a relative biological effectiveness (RBE) comparable to photons. Important steps in carbon ion technique are the development from passive to active beam delivery with intensity modulation, multiple beam optimization, and the introduction of gantry technology (HIT).

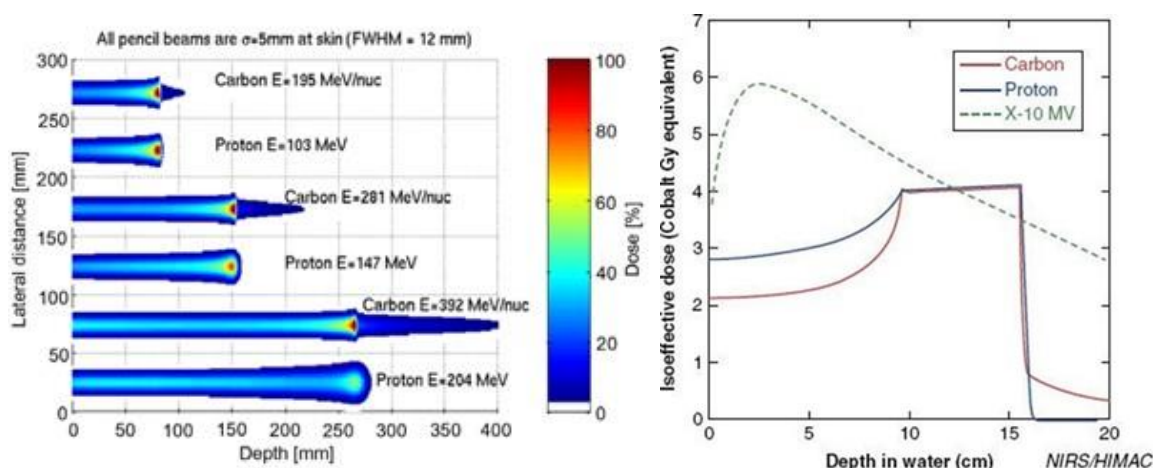


Figure 79: Carbon-ion characteristics

In addition to the physical advantages of particles, carbon ions have a biological advantage. The RBE (Relative Biological Effectiveness) of carbon ions varies. Although the RBE is low in the entrance channel, it increases at the end of the range. Increasing the dose per fraction leads to lower RBE of the tumour and the normal tissue. Nevertheless, the RBE of the tumour decreases more slowly than the RBE of the normal tissue. Hence, hypo-fractionated carbon ion treatment is often used in the carbon ion facilities to spare the organs at risk while escalating the dose to the tumour. Mathematical models for the RBE are developed and are applied in Germany (HIT, Marburg) and Italy (CNAO).

It is to note that the number of carbon ion facilities is increasing: 10 centres are operating at the beginning of 2018. The total number of patients treated until the end of 2016 was 21,580 (PTCOG website). In Europe four carbon ion centres are in operation: HIT (Heidelberg), MedAustron (Wiener Neustadt), MIT (Marburg), and CNAO (Pavia).

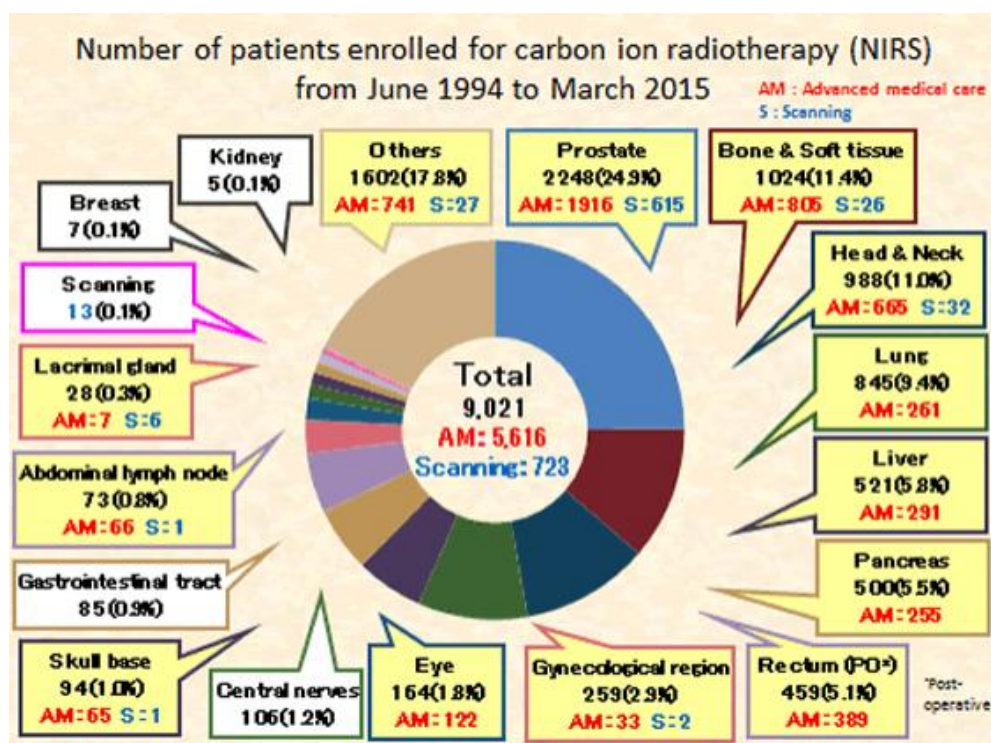


Figure 80: Number of patients enrolled for carbon ion radiotherapy (NIRS)

Although there is a good track-record of carbon-ion therapy (mainly thanks to Japanese experience²⁸⁸), but very few comparative studies have been performed to compare proton and carbon-ion therapy efficiencies. The first studies were conducted at NIRS, GSI and HIT focusing on dose and fractionation in relation with toxicity and tumour response assessment (phase I-II); now randomized clinical trials can be performed and a few are actually ongoing. Some studies were launched along with Proton therapy Development (*Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study*²⁸⁹, launched in 2010, results expected in 2017). There are two phase III trials (on low and intermediate grade chondrosarcoma of the base of skull), and 18 phase II trials registered at the NIH website (ClinicalTrials.gov).

Among these 18 trials, 5 of them have a randomized design (about prostate, sacral chordoma, glioblastoma, recurrent glioma, and meningioma). In addition are some results of carbon ion therapy very promising, especially in radio-resistant tumours (sarcoma, head and neck tumours such as denoid-cystic carcinoma and mucosal melanoma, hepatocellular carcinoma and high-risk prostate carcinoma) and deserve further investigation in clinical setting by controlled clinical trials. After evaluation of these results, the medical community has to decide whether the clinical benefit resulting from the dose-sparing potential of protons is high enough to justify the costs or whether the additional biological effect of heavy ions also has to be considered in the cost-effectiveness calculation.

At the moment, carbon-ion therapy is less competitive than proton therapy.

²⁸⁸ <http://www.ansto.gov.au/AboutANSTO/MediaCentre/News/ACS087287>

²⁸⁹ <https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-10-606>

Table 2.: Investment cost (€).

	C ion	Proton	Combined	One-room proton
Investments	Excl. VAT	Excl. VAT	Excl. VAT	Excl. VAT
Building	25,000,000	15,000,000	30,000,000	10,000,000
Equipment	50,000,000	25,000,000	60,000,000	20,000,000
Imaging	4,000,000	4,000,000	4,000,000	2,000,000
Simulation	2,000,000	2,000,000	2,000,000	1,000,000
Planning	1,000,000	1,000,000	1,000,000	1,000,000
Record & verify	500,000	500,000	500,000	500,000
Anaesthesia	0	1,500,000	1,500,000	1,500,000
Facilities	2,500,000	2,500,000	2,500,000	1,000,000
Total investments	85,000,000	51,500,000	101,500,000	37,000,000

Table 31 : Comparative Investment costs for Carbon Ion therapy, Proton therapy centres - Feasibility study of a Hadron Therapy Centre in Belgium (2013 – The Belgian Hadron Therapy Centre (BHTC) Foundation

A9. Other Therapeutic Applications

A.9.1. Boron Neutron Capture Therapy

The principle of BNCT is to irradiate tumours in a focused manner owing to a boron-10 containing pharmaceutical targeting the tumour and to the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction delivering α particles locally. This is “Targeted Alpha Therapy” (TAT).

For this therapy, a neutron source is mandatory.

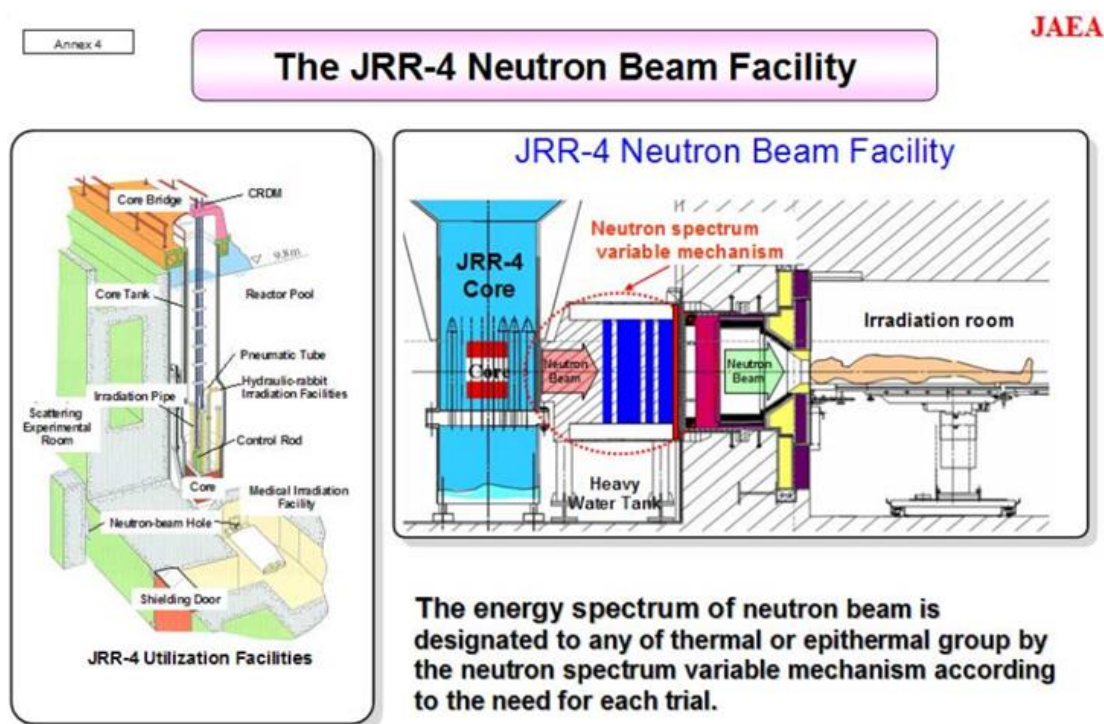


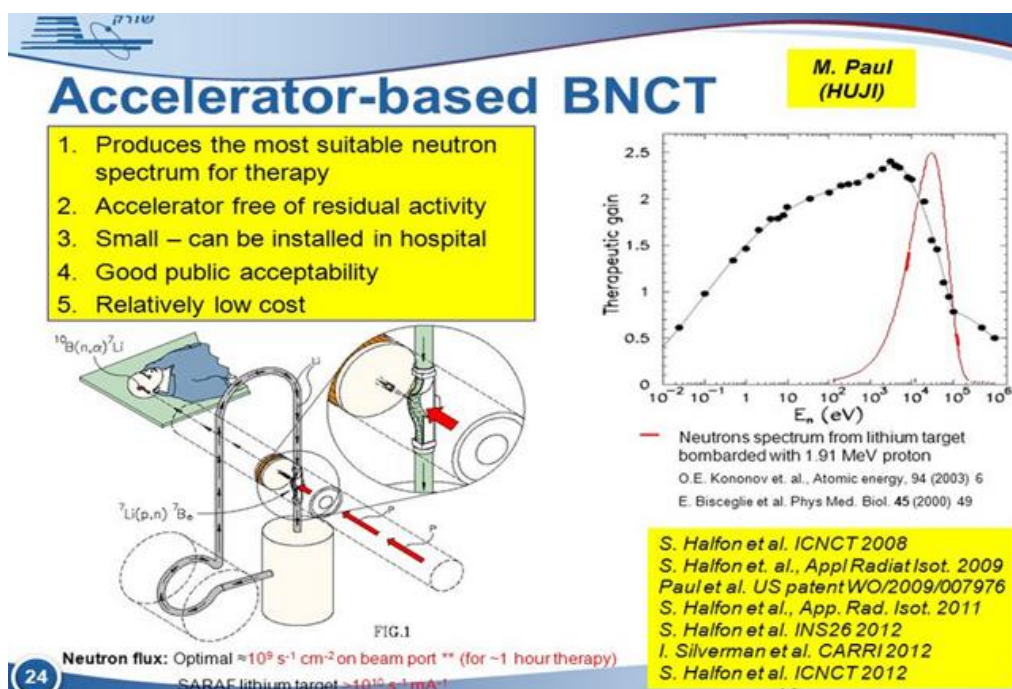
Figure 81 : The JRR-4 BNCT device

Around an existing reactor, the expenditures for designing and building a BNCT facility are moderate. At the FiR 1 (Finland/VTT, 250 kW Triga) they amounted to about €4 million (2007 figures), but BNCT breakthrough of the market remains difficult.

As of 2007, only close to 30 patients had been treated at the FiR 1 since May 1999. HFR Petten has the same experience of a very limited market.

Despite the treatment being technically interesting for more than 10 years, its cost and the attitude of the Health Insurance companies leave open a question for the BNCT Community: how to move forward?

New developments are nevertheless observed, based on accelerator technology.



The current projects are listed below:

Table 1 – Current status of the different accelerators intended for AB-BNCT facilities worldwide. Data displayed comprise institute and location, type of machine and its status, proposed target and reaction, beam energy and highest neutron energy, actual or necessary beam intensity and references.

Institute-location	Machine (status)	Target and reaction	Beam energy neutron energy (MeV)	Beam current (mA)	Reference
Budker Institute Russia	Vacuum insulated Tandem (ready)	Solid ${}^7\text{Li}(p,n)$	2.0 <1	2	Aleynik et al. 2011 ¹
IPPE-Obninsk Russia	Cascade generator KG-2.5 (ready)	Solid ${}^7\text{Li}(p,n)$	2.3 <1	3	Kononov et al. 2004 ²
Birmingham Univ. UK	Dynamitron (ready)	Solid ${}^7\text{Li}(p,n)$	2.8 <1.1	1	Ghani et al. 2008 ³
KURRI Japan	Cyclotron (clinical trials started)	${}^9\text{Be}(p,n)$	30 <28	1	Tanaka et al. 2011 ⁴
Soreq Israel	RFQ-DTL ^a (ready)	Liquid ${}^7\text{Li}(p,n)$	4 <2.3	2	Halfon et al. 2011 ⁵
INFN Legnaro Italy	RFQ (under construction)	${}^9\text{Be}(p,n)$	4-5 <2-3	30	Ceballos et al. 2011 ⁶
Tsukuba Japan	RFQ-DTL (under construction)	${}^9\text{Be}(p,n)$	8 <6	10	Kumada et al. 2011 ⁷
CNEA Buenos Aires Argentina	Single ended ESQ ^b Tandem ESQ (under construction)	${}^9\text{Be}(d,n)$ Solid ${}^7\text{Li}(p,n)$	1.4 2.5 <1	30 30	Kreiner et al. 2011, 2013 ⁸

^a RFQ-DTL stands for Radio Frequency Quadrupole-Drift Tube Linac.
^b ESQ means Electrostatic Quadrupole.

Table 32: Accelerator based BNCT projects

Whether such accelerator-based BNCT shall become the way for moving forward or not should be surveyed closely. Anyway, it is another illustration of the wealth of the accelerators applications.

A.9.2. VHEE

VHEE linac-based machines embraces the energy range 50 – 250 MeV and can deliver doses up to 20-30 Gy per second. Studies in the early 2000s have shown that VHEE therapy has the potential to be a better, yet cost-effective alternative to the photon therapy. Some potential advantages of this mode of radiotherapy over photon and proton therapy include:

- Better sculpting or conformal mapping –as there are minimal moving parts with electron scanning and beam steering is continuous.

- Rapid dose delivery –reduces necessity of preventing patient motion. In essence, physiological motion is frozen with this method –and indeed freezing the motion to less than one heartbeat should be feasible.
- Potentially better tumour control efficiency for the same dose.

Some recent simulations with 15 MeV photons showed significant perturbations of dose around an air cavity in the tissue, whereas simulations with 200 MeV electron beams showed negligibly small perturbations.

This therapy technique raises however challenges (high doses, dosimetry, etc.) and remains for now at the research stage.

A10. Radionuclide Imaging (SPECT/PET)

A.10.1. Foreword

A SPECT exam is based on the physical principle that several radioisotopes decay by emitting a γ radiation. A radioactive isotope, the tracer, which disintegrates by β^- emission or by electron capture is a potential candidate to be used for this exam. It is associated to a vector whose role is to target the cancerous cell on which it must cling.

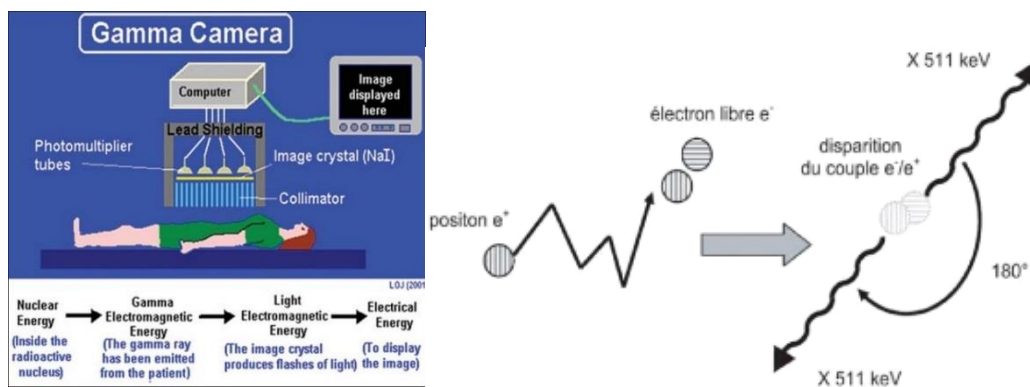


Figure 82: SPECT imaging principal

The radiotracer emits a γ photon that escapes from the patient and is detected by a γ camera. The camera transforms the radiation into an electrical signal and can interpret the position of the cancerous cells in the body. Technetium-99m is the most used (90% of the exams) because of its low cost and toxicity.

Contrary to the SPECT exam, PET uses radioisotopes decay by emitting a β^+ radiation i.e. positron emission. This particle is the total opposite of the electron. Rapidly after emission (positron travel 1 mm), they both meet and there is an annihilation. They disappear emitting two photons γ having the same energy (511 keV) in two opposite directions. They escape from the patient and are detected by a TEP camera that surrounds the patient. It allows a better detection than SPECT because the computer consider the detection valid only when it receives two photons at 180° from each other and at the same time.

PET and SPECT functional imaging are now most often associated with a CT anatomical scan that allows both imaging types at the same time. PET use increased in the EU-28 over the last decade, quickly becoming a complementary imaging solution to SPECT. Nevertheless, due to various constraints (surface limited in hospitals, limited health budgets...), a general tendency to replace some obsolete SPECT equipment by PET can be seen in Western EU. But SPECT is still widely used because of the low cost of Tc-99m (in comparison to F-18, for example) and the impossibility to perform certain imaging with PET (e.g. pulmonary scintigraphy).

A.10.2. Radionuclide imaging installed base

Radionuclide imaging brings a real benefit compared to Computed Tomography or MRI. It allows functional imaging, and direct location detection of tumours and cancerous cells based on a combination of radioisotopes and targeted molecules. Thus, interest continues to increase through the years.

PET and SPECT equipment today have complementary roles. PET allows more precise examinations at a higher cost, while SPECT remains very competitive with a wide range of applications (see next figure) through the use of Tc-99m. Through the last decade, the PET/SPECT number of exams ratio regularly increased, as the direct consequence of rapid growth of PET and SPECT stability.

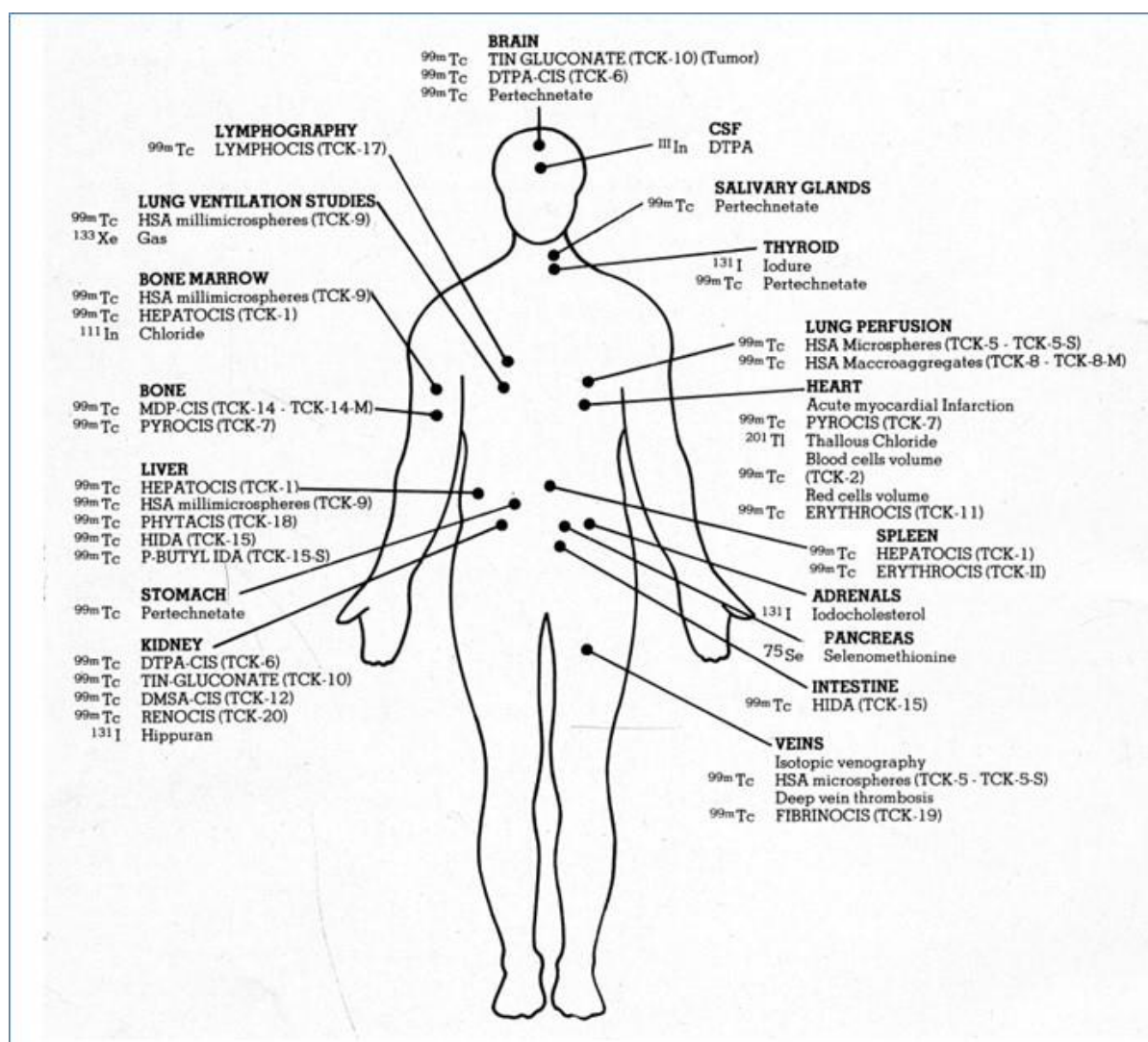


Figure 83: Tc-99m radiopharmaceuticals and their target-organs

TABLE A Age Evolution¹ of Installed Base vs. COCIR Golden Rules

		INSTALLED BASE				AGE VS 'GOLDEN RULES'		
		2008	2011	2013	2015	Mkt% by age 2013	Mkt% by age 2015	GOLDEN RULES
X-Ray Angiography	IB 1-5 years - units	2650	3811	3084	2361	43%	49%	60%
X-Ray Angiography	IB 6-10 years - units	1571	2163	2579	1641	36%	34%	30%
X-Ray Angiography	IB >10 years - units	1237	1780	1534	769	21%	16%	10%
X-Ray Angiography Total		5458	7754	7197	4771			
Computed Tomography	IB 1-5 years - units	6189	6569	5898	5669	50%	48%	60%
Computed Tomography	IB 6-10 years - units	3155	3627	4528	4574	38%	39%	30%
Computed Tomography	IB >10 years - units	933	1061	1477	1548	12%	13%	10%
Computed Tomography Total		10277	11257	11903	11791			
Magnetic Resonance Imaging	IB 1-5 years - units	3568	4287	4002	4081	47%	47%	60%
Magnetic Resonance Imaging	IB 6-10 years - units	2082	2546	2898	2947	34%	34%	30%
Magnetic Resonance Imaging	IB >10 years - units	808	1178	1653	1587	19%	18%	10%
Magnetic Resonance Imaging Total		6458	8011	8553	8615			
Molecular Imaging PET	IB 1-5 years - units	430	532	448	378	52%	49%	60%
Molecular Imaging PET	IB 6-10 years - units	118	294	325	332	38%	43%	30%
Molecular Imaging PET	IB >10 years - units	40	110	91	63	11%	8%	10%
Molecular Imaging PET Total		588	936	864	773			

1. Figures highlighted in red show deterioration in 2015 versus 2013

Figure 84: Age evolution of installed base of equipment (c) COCIR

COCIR data are directly coming from the industry (equipment vendors). A stable PET/SPECT market is indicated in COCIR SRI reports. COCIR figures were used preferentially for equipment installed base instead of Eurostat data.

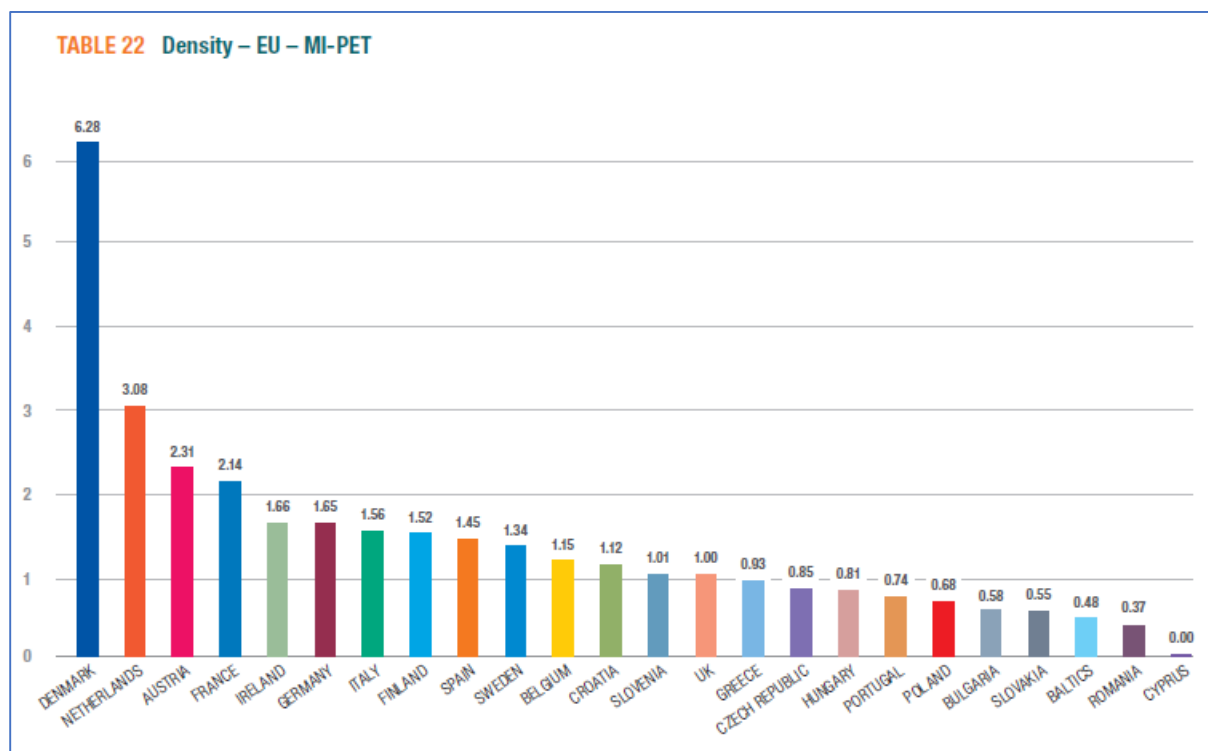


Figure 85: PET density (Equipment per Mhab) for EU Countries - Source COCIR

In this report, COCIR gives a series of indications on PET scan market:

- In Western Europe, in 2015, the average age of equipment decreased (compared to 2013), due a renewal of installed capacity in some countries (France and Greece extensively renewed their equipment, Sweden, UK, Belgium and Netherlands renewed their equipment with moderation, and the first countries to be equipped with PET are now using older equipment e.g. Norway, Germany, Ireland)
- In Western Europe, a small decrease of the average PET density (1.9 equipment per Mhab in 2013 compared to 1.7 in 2015)
- In Eastern Europe, a slight deterioration of age profile while equipment density remaining rather low as compared to EU-28 average

A.10.3. Number of procedures

It is interesting to try to build a picture of the past evolution of the number of procedures in Europe, in order to derive possible trends, as was tentatively made some years ago²⁹⁰.

Number of equipment and Imaging procedures (SPECT, PET, MRI, CT) over the European Union may be found in the Eurostat database. From this database the following data have been collected:

- ✓ Nb of gamma-camera in EU-28, evolution over 2010/2015 period;
- ✓ Nb of PET equipment and exams in EU-28, evolution over 2010/2015 period;
- ✓ Nb of MRI equipment and exams in EU-28, evolution over 2010/2015 period;
- ✓ Nb of CT equipment and exams in EU-28, evolution over 2010/2015 period;

For instance, for MRI:

²⁹⁰PRELIMINARY REPORT ON SUPPLY OF RADIOISOTOPES FOR MEDICAL USE AND CURRENT DEVELOPMENTS IN NUCLEAR MEDICINE.SANCO/C/3/HW D(2009) Rev. 8

		MRI											
		Nb of Equipments						Nb of Exams					
		2010	2011	2012	2013	2014	2015	2010	2011	2012	2013	2014	2015
Austria		156	157	161	163	168	179	no data	no data	no data	no data	no data	no data
Belgium		no data	no data	no data	no data	no data	no data	718370	774624	822242	860822	913420	964597
Bulgaria		31	46	54	53	51	51	no data	56560	47968	66405	50623	45430
Croatia		32	no data	42	45	44	47	no data	no data	142932	144869	160425	166572
Cyprus		16	17	17	17	17	17	5191	6261	6207	5939	5535	5823
Czech Republic		66	72	73	78	78	88	352380	408876	454199	475452	487435	505785
Denmark		no data	no data	no data	no data	no data	no data	337473	364038	374472	338372	423075	466600
Estonia		11	13	13	15	15	16	64485	61020	61917	67503	73261	64215
Finland		100	109	117	120	127	142	124764	131624	154102	167937	174279	214672
France		451	489	566	618	720	836	3903258	4397020	5364435	5970075	6329462	6983999
Germany		2211	2317	2305	2332	2470	2747	8624000	8874000	9270000	10018000	10637000	no data
Greece		255	no data	no data	266	no data	no data	no data	no data	750000	no data	no data	no data
Hungary		30	30	28	30	31	35	318350	327164	338370	343993	354216	374923
Ireland		56	60	57	61	62	66	no data	no data	no data	no data	no data	no data
Italy		1332	1435	1466	1518	1592	1715	no data	no data	no data	no data	no data	no data
Latvia		17	19	20	21	25	25	47112	60925	57743	64513	75637	84176
Lithuania		15	18	30	31	31	32	45522	72728	82817	99079	107312	118463
Luxembourg		7	7	7	7	7	7	38426	39773	41017	42875	43267	43459
Malta		3	2	3	4	5	5	no data	no data	9234	11965	16739	22166
Netherlands		203	215	198	193	217	212	815403	834384	no data	no data	864136	876864
Poland		179	184	209	258	251	290	no data	no data	885001	944115	1025446	1078793
Portugal		no data	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data
Romania		51	66	77	87	94	107	137480	140005	149500	177733	173684	222290
Slovakia		37	38	34	36	45	48	180390	187420	220966	230501	279562	307935
Slovenia		15	17	18	18	18	18	48904	64563	68231	74578	76062	87414
Spain		558	643	691	715	721	737	2775004	2945049	3019026	3241275	3597706	3637973
Sweden		no data	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data
United Kingdom		411	441	456	462	467	467	no data	no data	no data	no data	no data	no data

Figure 86: MRI Statistics in the EU - Eurostat

As can be seen, the coverage of the EU-28 is only partial, thus assumptions for the missing data has to be performed. Diverse approaches have been used:

- ✓ When data exist for a country, but with minor gaps, linear interpolation has been used;
- ✓ When data are available for equipment and not for procedures, or vice-versa, an average number of exams per equipment has been calculated country per country (and for EU-28 weighted with population) and used for conversion purpose;

- ✓ When data are limited (*only one value on the period 2010-2015*), a constant value has been used for the whole period;

This approach yields the table below

MRI													
	Nb of Equipments						Nb of Exams						
	2010	2011	2012	2013	2014	2015	2010	2011	2012	2013	2014	2015	
Austria	156	157	161	163	168	179	522149	525496	538885	545579	562314	599133	
Belgium	215	231	246	257	273	288	718370	774624	822242	860822	913420	964597	
Bulgaria	31	46	54	53	51	51	32576	56560	47968	66405	50623	45430	
Croatia	32	37	42	45	44	47	110500	127766	142932	144869	160425	166572	
Cyprus	16	17	17	17	17	17	5191	6261	6207	5939	5535	5823	
Czech Republic	66	72	73	78	78	88	352380	408876	454199	475452	487435	503785	
Denmark	101	109	112	101	126	139	337473	364038	374472	338372	423075	466600	
Estonia	11	13	13	15	15	16	64485	61020	61917	67503	73261	64215	
Finland	100	109	117	120	127	142	124764	131624	154102	167937	174279	214672	
France	451	489	566	618	720	836	3903258	4397020	5364435	5970075	6329462	6983999	
Germany	2211	2317	2305	2332	2470	2747	8624000	8874000	9270000	10018000	10637000	11182764	
Greece	255	259	262	266	270	273	729034	739517	750000	760483	770966	781449	
Hungary	30	30	28	30	31	35	318350	327164	338370	343993	354216	374923	
Ireland	56	60	57	61	62	66	187438	200827	190785	204174	207521	220909	
Italy	1332	1435	1466	1518	1592	1715	4458349	4803102	4906862	5080912	5328598	5740292	
Larvia	17	19	20	21	25	25	47112	60925	57743	64513	75637	84176	
Lithuania	15	18	30	31	31	32	45522	72728	82817	99079	107312	118463	
Luxembourg	7	7	7	7	7	7	38426	39773	41017	42875	43267	43459	
Malta	3	2	3	4	5	5	10388	6925	9234	11965	16739	22166	
Netherlands	203	215	198	193	217	212	815403	834384	792790	772770	864136	876864	
Poland	179	184	209	258	251	290	702541	722165	885001	944115	1025446	1078793	
Portugal													
Romania	51	66	77	87	94	107	137480	140005	149500	177733	173684	222290	
Slovakia	37	38	34	36	45	48	180390	187420	220966	250501	279562	307935	
Slovenia	15	17	18	18	18	18	48904	64563	68231	74578	76062	87414	
Spain	558	643	691	715	721	737	2775004	2945049	3019026	3241275	3597706	3637973	
Sweden													
United Kingdom	411	441	456	462	467	467	1375662	1476075	1526282	1546364	1563100	1563100	
TOTAL	6558	7031	7262	7506	7925	8588	26665149	28347907	30275983	32276283	34300781	36359795	

Figure 87: MRI statistics in the EU after retreatment- Eurostat

With this methodology the following coverage rate (EU-28 population) is obtained:

	Nb of Equipment	Nb of Exams
MRI	96% coverage	96% coverage
PET	81% coverage	81% coverage
SPECT	65% coverage	/
CT	96% coverage	96% coverage

Data uncertainties & coherence check

Data gathered through Eurostat Databases (*Number of examinations*²⁹¹ and *Number of Equipment*²⁹²) and RP180 (*through DDM2 initiative*) have to be considered with caution, as variations exist between these two sources.

RP180 data cover whole EU-28, but are stemming from various sources (survey, national data from statistics agencies...) and for different years; whereas Eurostat data are provided by national statistics agencies, with gaps in terms of countries and year covered. The differences are illustrated below for CT and PET.

The number of CT procedures in EU-28 is directly given in Eurostat, and can be compared with RP180 (*Number of Examinations per MHab*):

Number of CT Examinations...	RP 180	Eurostat (2012)	Difference
...for 21 countries, (i.e. 76% of EU population, Eurostat dataset)	35 525 254	41 321 772	+16%
...for EU-28	49 302 690	/	
...with extrapolation for EU-26* with 4012 exams per equipment per year (weighted with previous EU-21 nb of Equipment)	/	50 798 221	+3%
*Portugal and Sweden missing, i.e. 4% of EU population			

²⁹¹ http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_co_exam&lang=en

²⁹² http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_rs_equip&lang=en

	Total PET EXAMS	
	RP 180	EUROSTAT (2012)
Austria	11 500	
Belgium		
Bulgaria	2 579	
Cyprus		
Czech republic		33 732
Germany	82 700	130 200
Denmark	22 468	29 708
Estonia	532	
Greece	4 559	
Spain	63 947	97 068
Finland	3 027	1 244
France	113 705	
Croatia	6 559	7 226
Hungary	11 281	13 482
Ireland		
Italy		
Lithuania		34
Luxembourg	1 718	1 825
Latvia		
Malta		480
The Netherlands		41 581
Poland	11 480	32 059
Portugal	16 590	
Romania		3 153
Sweden	8 271	
Slovenia	3 342	
Slovakia		5 255
United Kingdom	11 175	
TOTAL	375 432	397 047

Extrapolations may be done for covering EU-28, but they must be done cautiously. In the CT case, similar results are obtained with Eurostat and RP180 dataset (~5-10% error margin).

Same kind of difficulties exist for the number of PET procedures as can be seen in the next table. Number of procedures are comparable between RP180 and Eurostat (year 2012) but this hides differences because the two figures do not cover the same countries.

In addition, it is unclear whether the definitions in the different countries are homogeneous (for instance are PET/CT included in PET or in CT or, more important, are planar scintigraphy included or not in the declared SPECT procedures?).

Despite the difficulty to gather reliable, complete and homogeneous data for EU-28 over the last decade, Eurostat database may be used (with caution) in order to detect trends for the different Imaging Technologies (MRI, PET, CT).

With the above assumptions and precautions, it is possible to build from Eurostat data quantitative historical curve like the ones below :

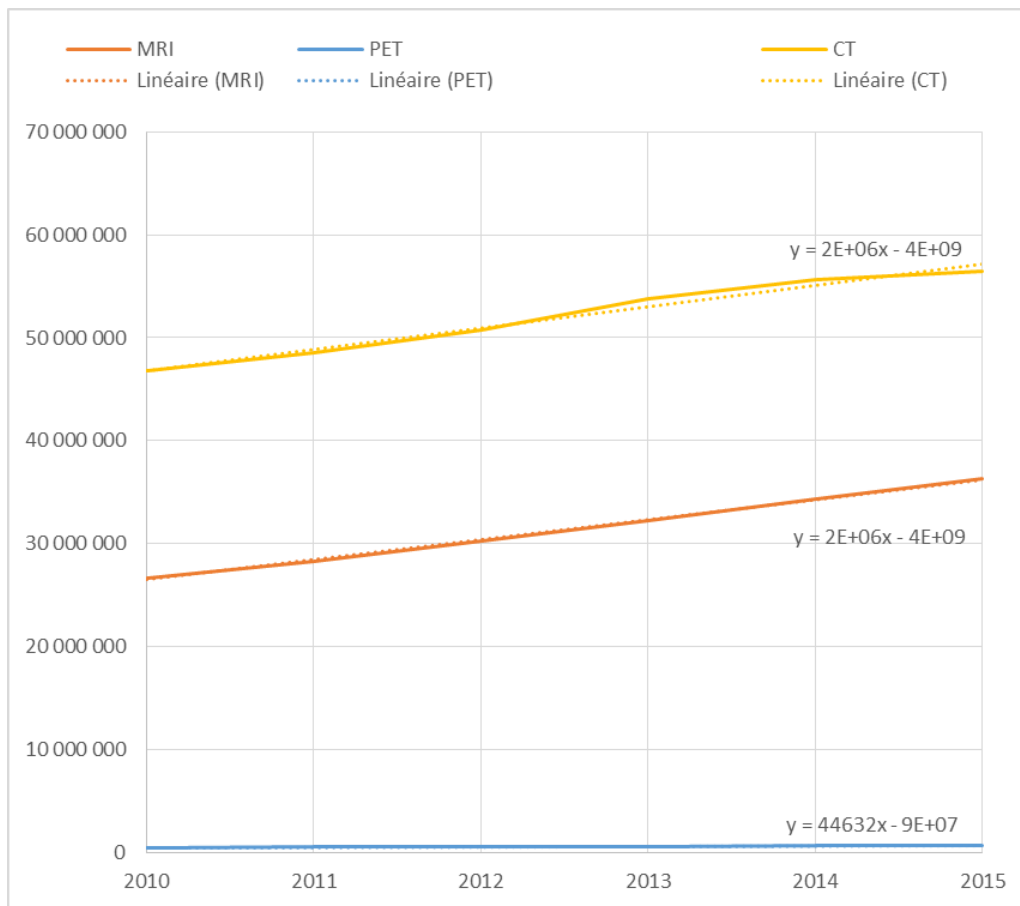


Figure 88: Number of procedures (data extrapolated from Eurostat)

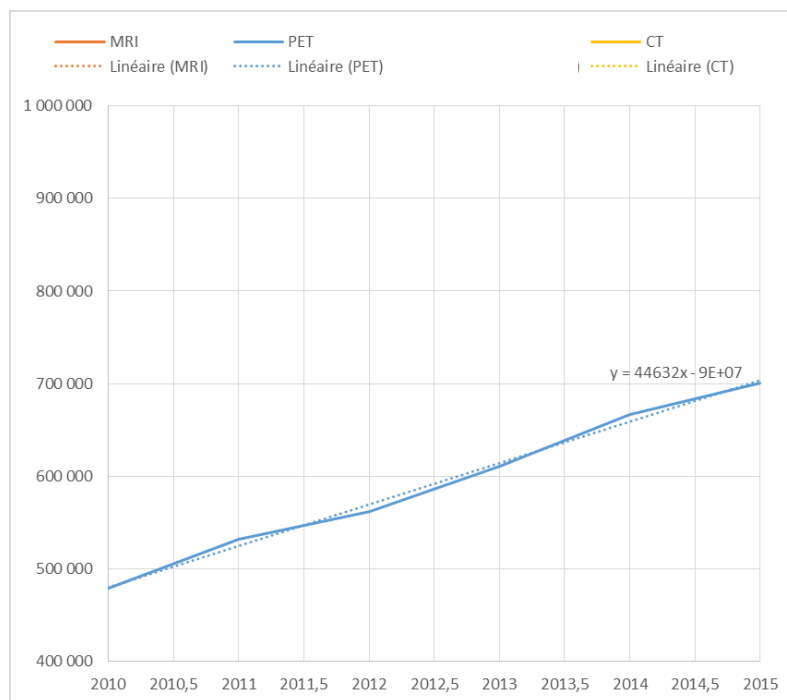


Figure 89: Zoom on number of PET procedures – data extrapolated from Eurostat)

From the Eurostat data above, it is possible to draw the conclusions that:

- CT (resp. MRI) procedures are constantly increasing and are now over 55 million (resp. 35 million) annually in EU-28
- PET procedures are constantly increasing and amount to about 700 000 in EU-28

Unfortunately, the Eurostat data relatively to the number of SPECT procedures are not available. In the RP180 survey (2012), Tc-99m procedures per number of people are given.

	Nr of NM imaging procedures/Mhab per Isotope										Population Mhab RP 180	Diagnostic NM Procedures	of which Tc- 99m procedures
	Tc	TI	I131	I123	Ga 67	In 111	F 18	O15	Other	Sum			
Austria	13 060	881	0	0	0	0	1 369	0	0	15 310	8,4	128 604	109 704
Belgium	na	na	na	na	na	na	na	na	0	0	10,87	0	
Bulgaria	2 163	0	89	14	0	0	342	0	0	2 608	7,54	19 664	16 309
Cyprus	5 631	286	7	0	6	8	0	0	0	5 938	0,84	4 988	4 730
Czech republic	8 995	24	nc	nc	0	28	0	nc	0	9 047	10,5	94 994	94 448
Germany	31 385	471	na	379	1	na	987	24	2 445	35 692	81,8	2 919 606	2 567 293
Denmark	14 576	0	91	204	0	100	3 963	78	0	19 012	5,56	105 707	81 043
Estonia	2 389	0	73	60	0	0	403	0	0	2 925	1,32	3 861	3 153
Greece	16 927	5 496	443	na	135	47	416	0	0	23 464	10,96	257 165	185 520
Spain	11 171	0	158	340	219	128	1 360	0	0	13 376	47,02	628 940	525 260
Finland	4 566	168	101	199	0	32	543	25	0	5 634	5,33	30 029	24 337
France	15 624	1 635	38	492	53	74	1 785	0	0	19 701	63,7	1 254 954	995 249
Croatia	7 656	92	193	143	79	23	1 529	0	0	9 715	4,29	41 677	32 844
Hungary	13 649	46	64	1	13	30	1 127	0	0	14 930	10,01	149 449	136 626
Ireland	6 693	0	92	124	0	46	0	0	0	6 955	3,45	23 995	23 091
Italy	11 115	79	397	490	80	61	2 206	na	0	14 428	60,63	874 770	673 902
Lithuania	4 795	0	48	0	0	0	0	0	0	4 843	3,25	15 740	15 584
Luxembourg	30 511	28	468	1 336	32	1 543	3 655	0	0	37 573	0,47	17 659	14 340
Latvia	4 979	0	627	9	0	0	0	0	0	5 615	2,07	11 623	10 307
Malta	9 242	0	126	12	40	10	0	0	0	9 430	0,41	3 866	3 789
The Netherlands	10 362	11	3	481	0	0	798	nc	0	11 655	16,49	192 191	170 869
Poland	2 981	0	1 426	0	2	0	301	0	0	4 710	38,14	179 639	113 695
Portugal	16 576	72	120	62	66	26	1 571	0	0	18 493	10,56	195 286	175 043
Romania	436	0	28	63	0	0	0	0	0	527	21	11 067	9 156
Sweden	6 965	1	2	112	0	103	899	0	0	8 082	9,2	74 354	64 078
Slovenia	12 800	122	123	244	7	129	1 630	0	0	15 055	2,05	30 863	26 240
Slovakia	5 507	na	na	29	3	35	726	na	0	6 300	5,44	34 272	29 958
United Kingdom	7 966	264	31	37	15	23	182	0	0	8 518	61,4	523 005	489 112
TOTAL												7 827 968	6 595 681

Table 33: Number of NM procedures (RP180 2012)

In this table, Belgium is missing and is a large NM user. Hence, according to RP 180, this would mean that PET + SPECT²⁹³ (Tc-99m) represent annually more than 0,7 + 6,6 = 7,3 million procedures in EU-28, of which about 10% are PET procedures.

However, inconsistencies appear when comparing detailed countries data with the data above. Indeed, in the next paragraph, we present German and French figures. Whereas French figures above are coherent with more recent data, it is not the case for Germany, where RP180 reports about 3 million NM procedures and the most recent data about 2 million. Explanation of these discrepancies remain unclear.

On the other hand, the number of SPECT equipment may be found in Eurostat database as seen previously. According to these data, the number of gamma cameras (SPECT)

²⁹³Figure likely comprising planar scintigraphies.

seems to remain roughly constant over EU-28 and over the years. However, it is hazardous to derive a correlation between number of SPECT equipment and number of procedures.

A.10.4. Country highlight: Situation in Germany

As seen above, it is difficult to get reliable statistics for the different imaging procedures using radioisotopes. However, an interesting study has recently been performed in Germany²⁹⁴. In Germany, two main sectors are distinguished, ambulatory/private (“vertragsärztlichen Versorgung”) and hospitals (“Stationärer Bereich”). Both are performing Nuclear medicine procedures. The relative part of both is depicted below, as well as the total number of NM procedures:

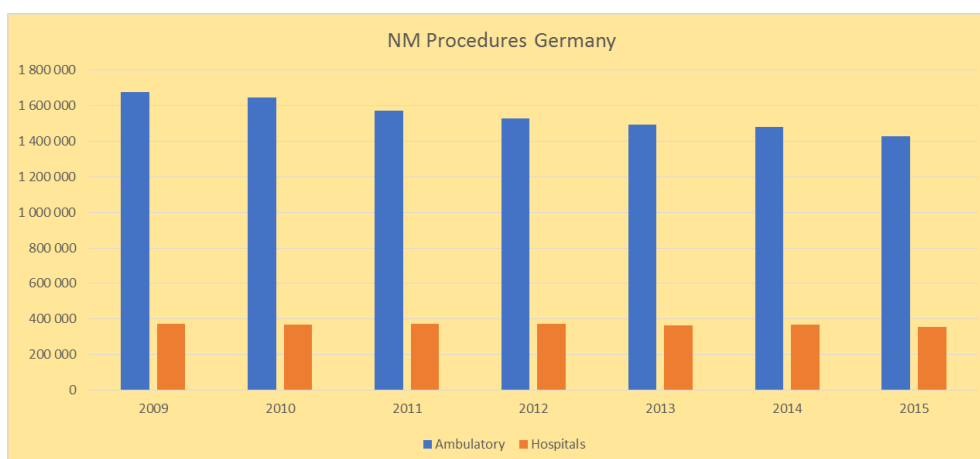


Figure 90: Number of NM procedures in Germany

Details on the nature of the procedures in the “vertragsärztlichen Versorgung” (ambulatory/private) sector (in blue above, the most important) is unfortunately not available. However, for the “Stationärer Bereich” (hospitals, in orange), split among Planar scintigraphy, SPECT, SPECT/CT, PET and PET/CT is available. The corresponding figures are given below:

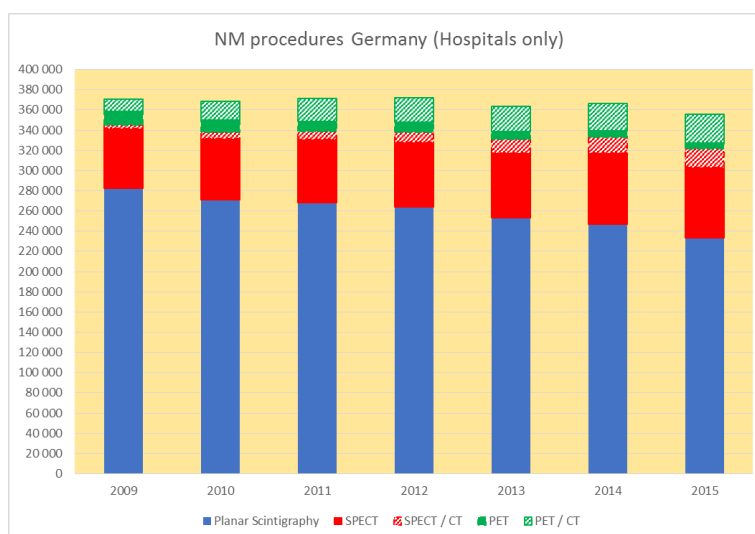


Figure 91: NM Procedures by type in Germany (Hospitals)

²⁹⁴ Nuklearmedizin in Deutschland Aktualisierte Kennzahlen und Trends aus offiziellen Statistiken; Dirk Hellwig; Jörg Marienhagen; Karin Menhart; JirkaGrosse. Nuklearmedizin 2/2017

And more precisely:

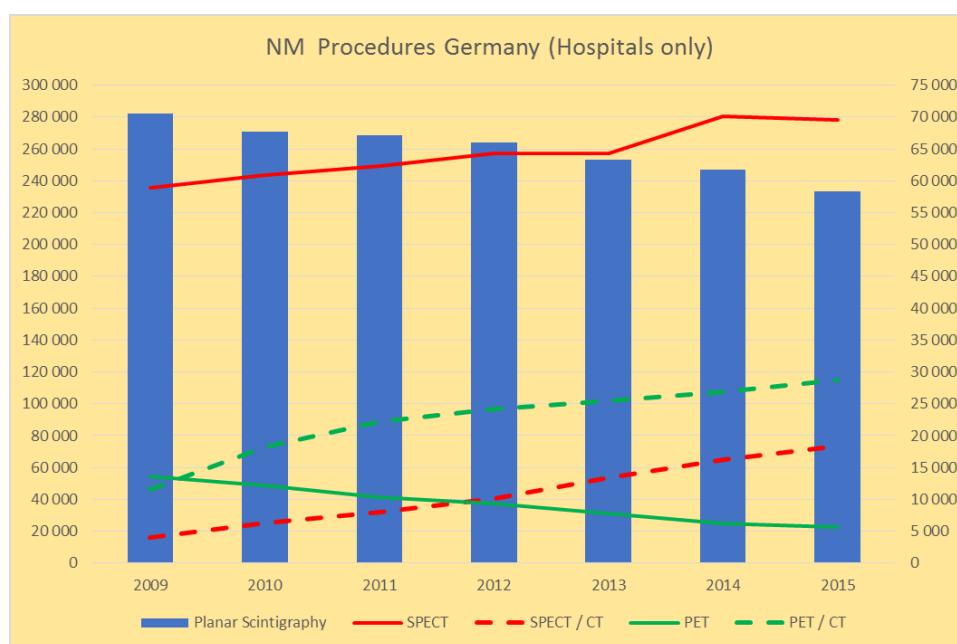


Figure 92: NM procedures by type in Germany (bars scale on the left, lines scale on the right) - Hospitals

From these 3 figures, we see that:

- The total number of NM procedures is slightly decreasing in the observed 7-years period
- Planar scintigraphy²⁹⁵ is constantly declining,
- SPECT and SPECT/CT are constantly increasing
- PET is decreasing, replaced a rather constant rate by PET/CT

The “StationärerBereich” of Germany represents about 360 000 procedures, i.e. about 4% of the European total. Such a ratio is rather a low ratio for allowing an extrapolation, but the figures above show long term trends:

- Planar scintigraphy decrease is probably due to the replacement of old equipment by new ones
- SPECT is not declining at all, amplified by the SPECT/CT development. It is interesting to note that the effect of Mo-99 shortage in years 2008/2009 is hardly noticeable on these figures
- PET examinations are rather constant, “single” PET being aggressively replaced by PET/CT

Reimbursement practices also have an important impact on technology use and development. PET reimbursement remains low in Germany compared to other EU Western countries, limiting PET development.

A preliminary interpretation of these trends has been kindly provided by Pr.-Dr.Hellwig²⁹⁶, the author of the study reported above:

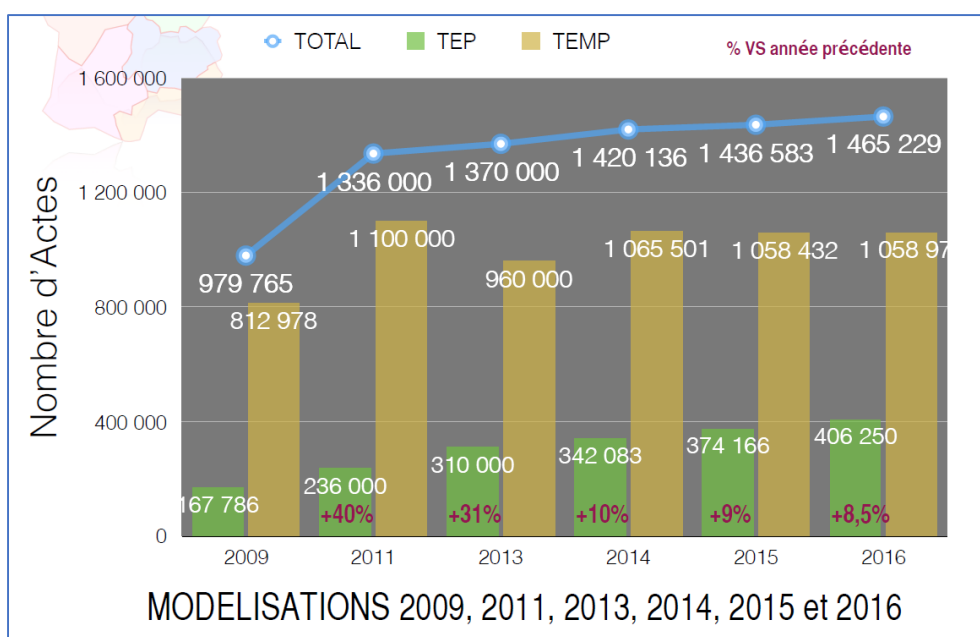
²⁹⁵ Words have not the same sense in all MS : “scintigraphie” covers all procedures with radioisotopes in France. It is apparently not the case in Germany.

²⁹⁶ Univ.-Prof.Dr. Dirk Hellwig Nuklearmediziner, Diplom-Physiker Leiter der Abteilung für Nuklearmedizin Universitätsklinikum Regensburg, Germany

1. Reduction of "Planar scintigraphy" compensated with SPECT + SPECT/CT increase.
This may be related to the change in habits of nuclear medicine physicians using more SPECT as acquisition technique instead of planar scintigraphy. The increasing use of SPECT/CT is related to the availability of this new equipment. In addition, clinical guidelines changed and more consequently lung perfusion scans are used to exclude pulmonary embolism.
2. PET + PET/CT seems rather constant, contrary to SPECT + SPECT/CT which increases. There is limited reimbursement for PET and PET/CT in Germany as compared to the rest of Europe. For out-patients, only a few indications are covered by statutory health insurance like "evaluation of solitary pulmonary nodules, if biopsy is not possible", "preoperative staging of non-small cell lung cancer", "recurrent non-small cell lung cancer" or "Hodgkin's disease after chemotherapy with a 1.5 cm lymphoma remnant in contrast-enhanced CT to decide about irradiation". For in-patients, all days stayed in hospitals for a PET scans are usually eliminated from the number of days counted for reimbursement. Consequently, there is very limited access to PET or PET/CT with unclear financing except for patients with private health insurance. On the other hand, SPECT and SPECT/CT can be charged for based on existing reimbursement structures without further limitations. Currently, some first signs of improvement for broader PET reimbursement can be seen in Germany, but this will take time.
3. Could these trends be extrapolated to EU-28? The development of clinical indications for nuclear medicine procedures will mainly affect the extrapolation to EU-28. The German trends for non-PET could probably (to be confirmed) be extrapolated to EU-28 whereas a boost of PET in Germany is predictable, as Germany is the red lamp of (western) Europe with respect to PET utilisation under indications needed for patient care.
4. Possible evolutions of NM? We will see a trend to more PET/CT and SPECT/CT examinations as well as new theranostic applications with nuclear medicine as we currently experience with prostate cancer care based on PSMA-tracers used for diagnosis (e.g. Ga-68-PSMA-11) and treatments (e.g. Lu-177-PSMA-617).

A.10.5. Country highlight: Situation in France

SFMN realizes every year a survey relatively to NM procedures. The trend is shown below.



On this figure French acronym "TEP" stands for PET and "TEMP" stands for SPECT.

Figure 93: Number of procedures in France

From the above, SFMN derives the following conclusions:

- PET annual growth is about 9% since 2013
 - o FDG $\approx$ 94 % of uses
 - o FCH (choline): 2nd tracer after FDG (x 300% between 2013 and 2016) (>15 000 doses)
- SPECT procedures are stable, slightly greater than 1 million procedures/year
 - o Clinical indications: $\approx$ 40 % Bones, $\approx$ 33 % Heart; Lungs indications are stable (60 000 procedures/year)
 - o Increase of SPECT/CT: + 100 000 procedures since 2014 (+10% of total NM procedures)
 - o Number of gamma cameras stable, but increase of hybrid cameras
- Therapeutic activity remains stable (<1% of the procedures): thyroid represents 91% of indications.

General conclusion from France and Germany case studies

According to the figures above, France and Germany represent together about 3 million procedures/year, that is to say about 30% of EU-28 procedures if we assume a total of 10 million procedures in EU-28²⁹⁷. Such a ratio is statistically not sufficient to extrapolate tendencies to EU-28. But the similar tendencies in France and Germany suggest an important presumption, that would need to be verified over EU-28, through an in-depth specific assessment of PET/SPECT exams evolutions. As data is not publicly

²⁹⁷the population ratio F+D/EU-28 is slightly less than 30%. Explanation could lie with the apparent high number of scintigraphies in Germany. To be checked.

available, or even collected on a national basis, a preliminary work of data collection with each EU-28 competent authority is recommended to dispose of reliable dataset:

SPECT is a least stable, PET + PET/CT should increase (Stability of PET + PET/CT in Germany is suspected to be an anomaly due to the reimbursement system). SPECT/CT and PET/CT progressively replace SPECT and PET.

A.10.6. Radiation protection issue

Since 2010, much emphasis has been placed on reducing radiation dose from CT exams. While radiologists and others still debate the extent of the risk of repeated CT scans, societies and equipment manufacturers have been working diligently to reduce unnecessary exposure from CT. However, PET and SPECT scans and SPECT can expose patients to even more ionizing radiation than CT alone, but less SPECT/PET exams are performed, which explain the focus on CT in the last years. The effective dose received by a patient during a SPECT or PET examination depends on several factors: the radiotracer used (Tc-99m, In-111, Ga-68, I-131 ...), the associated molecule (Tc-99m-MIBI, Tc-99m-MDP ...) the targeted organ (brain, liver, kidneys, heart ...), or the technological efficiency of the equipment. In general, the contribution of nuclear medicine to the effective per capita dose is rather low compared to X-ray technologies²⁹⁸.

Some studies have attempted to estimate the doses received by the organs subjected to these imaging techniques and to compare them with the dose delivered by the CT scan. The dose delivered to organs such as liver, kidneys or brain from a PET exam alone, using ¹⁸F¹⁸FDG is about 5 mSv²⁹⁹. Similarly, an SPECT whole body imaging study induces an effective dose of 4.2 mSv using Tc-99m-MDP, 8.3 mSv with Tc-99m-MIBI or 2.4 mSv with ¹²³I-MIBG³⁰⁰. In addition, the latter study estimates that the combination of CT with SPECT increases the effective dose by 27 to 125% compared to SPECT alone.

The same types of technological advances detailed in computed tomography section (iterative reconstruction, detectors improvements, switch from analogic to digital detectors...) will improve PET³⁰¹ and SPECT efficiency, thus allowing to deliver lower dose to patients.

²⁹⁸ IRSN, «Exposition de la population française aux rayonnements ionisants liée aux actes de diagnostic médical en 2012,» & European Commission, «Medical Radiation Exposure of the European Population,» 2014.

²⁹⁹ A. Kaushik, «Estimation of radiation dose to patients from ¹⁸F¹⁸FDG whole body PET/CT investigations using dynamic PET scan protocol» INDIAN J MED RES, December 2015.

B. Huang, «Whole-Body PET/CT Scanning: Estimation of Radiation Dose and Cancer Risk» Radiology (RSNA), April 2009.

³⁰⁰ A. Mhiri, «Estimation of Radiation Dosimetry for some Common SPECT-CT Exams» International Journal of Biotechnology for Wellness Industries, 2012.

³⁰¹ <http://www.radiologytoday.net/archive/rt0115p22.shtml>

A.10.7. Tc-99m SPECT substitution

In the last decade, after the 2008-2009 shortage of Tc-99m, several national bodies among EU worked on the definition of the strategy to adopt in case of a new and extended shortage. It enables to identify the substitution margin of Tc-99m, along with its main drawbacks (*cost, examinations quality...*). The French Medicine Academy³⁰² identified for example 6 indications for which Tc-99m currently cannot be replaced: sentinel lymph node determination for cancer surgery, pulmonary embolism for pregnant women, all the patients with allergy to radiological contrast agents (diabetic patients), hyperparathyroidism, bone scintigraphy for kids and kidney function investigations. All these indications represent roughly 10% of SPECT Exams performed.

Alternatives exist for the main indications for Tc-99m SPECT imaging, but it generates important cost overruns and dose increase for the patient. For example, the Tc-99m bone scintigraphy (~35% of exams) can be replaced with Sodium Fluoride PET scan with a higher cost, myocardial scintigraphy (~20% of exams) can be replaced by Thallium 201 with a higher cost and dose received by the patient (for dedicated Heart Gamma Camera, dose received is equivalent).

Although Tc-99m SPECT appears to be the preferred “technical” solution only for a minor series of indications, the main obstacle for Tc-99m substitution remain the cost of alternatives. For economic reasons, Tc-99m SPECT use should remain high in the next years as long as the gap cost remain high with its alternatives.

³⁰² ACADEMIE NATIONALE DE MEDECINE - Communiqué, 18 février 2014

A11. Radioisotope supply chain

Radioisotopes are largely used in medicine for imaging. The Positron Emission Tomography (PET) needs radioisotopes decaying by positron emission (β^+ particle) whereas the Single Photon Emission Computed Tomography (SPECT) simply requests radioisotopes emitting gamma radiation directly measured (β^- emitters, electronic capture). There are dozens of medical radioisotopes that can be employed but the main ones are listed in the following table. The list is similar to the imaging radioisotopes, which are currently reimbursed by Belgium Government (*Inami*³⁰³).

Radioisotopes		Half-life	Imaging	Main Supply Chain*	
				Reactor	Cyclotron
C-11	Carbon-11	20 min	PET		X
Cr-51	Chromium-51	28 d	SPECT	X	
F-18	Fluorine-18	110 min	PET		X
Ga-67	Gallium-67	3,3 d	SPECT		X
Ga-68	Gallium-68	78 hr	PET		(X)
I-123	Iodine-123	13 hr	SPECT		X
I-131	Iodine-131	8 d	SPECT	X	
In-111	Indium-111	2,8 d	SPECT	X	
Kr-81m	Krypton-81m	13 s	SPECT		(X)
N-13	Nitrogen-13	10 min	PET		X
O-15	Oxygen-15	2 min	PET		X
Se-75	Selenium-75	120 d	SPECT	X	
Tc-99m	Technicium-99m	6 hrs	SPECT	(X)	
Tl-201	Thallium-201	73 hr	SPECT		X

Belgian RI reimbursement base (INAMI)

* (X) corresponds to RI produced through decay of a generator. The production approach for parent RI is given
Table 34 : Radioisotopes reimbursed by INAMI (Belgium)

The different RI used for imaging purpose (*or their parents in the case of a RI Generator*) are either produced in reactor or cyclotron. As of today, the two main RI used for imaging purposes are Tc-99m (for SPECT) and F-18 (for PET), which represent more than 90% of the RI imaging examinations³⁰⁴.

The figure below gives the breakdown between reactor and cyclotron production for typical Radioisotopes used in the health Sector.

³⁰³ List of refundable radiopharmaceuticals - INAMI

³⁰⁴ <https://ec.europa.eu/energy/sites/ener/files/documents/RP180.pdf> - Table 5.24. Annual frequencies of diagnostic NM examinations in European countries, per million of population, according to the isotope used

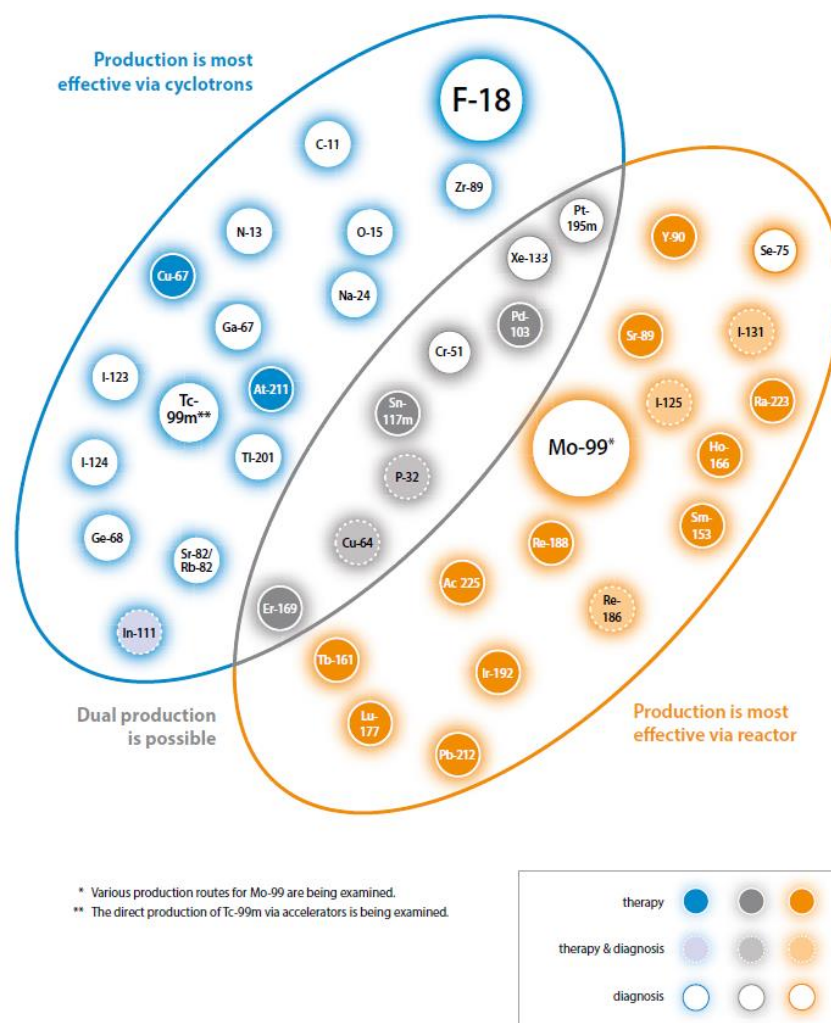


Figure 94 : Way of producing the radioisotopes used in the Health domain

The table below depicts the production reactions of the radioisotopes used in the Health sector.

Symbol	Radioisotopes	Half-life	Production process	Imaging	Therapy	Generator	Parent of...
Production via cyclotron or reactor	Cr-51	Chromium-51 (28 d)	$^{50}_{24}\text{Cr} + n \rightarrow ^{51}_{24}\text{Cr}$ $^{51}_{23}\text{V} + p \rightarrow ^{51}_{24}\text{Cr} + n$ neutron activation of Chromium-50 (stable)	SPECT			
	Cu-64	Copper-64 (12,7 hr)	$^{63}_{29}\text{Cu} + n \rightarrow ^{64}_{29}\text{Cu}$ $^{64}_{28}\text{Ni} + p \rightarrow ^{64}_{29}\text{Cu} + n$ Neutron irradiation of natural copper 63 or proton bombardment of Ni-64 target	SPECT	X		
	Er-169	Erbium-169 (9,4 d)	$^{168}_{68}\text{Er} + n \rightarrow ^{169}_{68}\text{Er}$ Neutron irradiation of enriched Erbium-168 target		X		
	P-32	Phosphorus-32 (14 d)	$^{31}_{15}\text{P} + n \rightarrow ^{32}_{15}\text{P}$ $^{32}_{16}\text{S} + n \rightarrow ^{32}_{15}\text{P} + p$ $^{32}_{16}\text{S} + ^2_1\text{D} \rightarrow ^{32}_{15}\text{P} + 2p$ direct neutron irradiation of P-31 or S-32 or deuterons bombardment of Sulfur32	SPECT	X		
	Pd-103	Palladium-103 (17 d)	$^{103}_{45}\text{Rh} + p \rightarrow ^{103}_{46}\text{Pd} + n$ $^{103}_{45}\text{Rh} + ^2_1\text{D} \rightarrow ^{103}_{46}\text{Pd} + n$ $^{102}_{46}\text{Pd} + n \rightarrow ^{103}_{46}\text{Pd}$ Rhodium-103 protons or deuterium bombardment Or neutron irradiation of Pd-102		X		
	Pt-195m	Platinum-195m (4 d)	$^{194}_{78}\text{Pt} + n \rightarrow ^{195\text{m}}_{78}\text{Pt}$ $^{192}_{76}\text{Os} + \alpha \rightarrow ^{195\text{m}}_{78}\text{Pt} + n$ Neutron irradiation of Platinum-194 or bombardment of Osmium-192 with alpha particles	SPECT			
	Sn-117m	Tin-117m (13,6 d)	$^{116}_{50}\text{Sn} + n \rightarrow ^{117\text{m}}_{50}\text{Sn}$ $^{117}_{50}\text{Sn} + n \rightarrow ^{117\text{m}}_{50}\text{Sn} + n$ $^{116}_{48}\text{Cd} + \alpha \rightarrow ^{117\text{m}}_{50}\text{Sn} + 3n$ Neutron irradiation of Tin 116 or 117 Or alpha bombardment of Cadmium-116		X		
	Xe-133	Xenon-133 (5,2 d)	$^{235}_{92}\text{U} + n \rightarrow ^{236}_{92}\text{U}^* \rightarrow ^{133}_{54}\text{Xe} + n + X$ Neutron bombardment : fission of uranium-235 (U-235)	X			

	Symbol	Radioisotopes	Half-life	Production process	Imaging	Therapy	Generator	Parent of...
Production via cyclotron	At-211	Astatine-211	(7,216 h)	$^{209}_{83}\text{Bi} + \alpha \rightarrow ^{211}_{85}\text{At} + 2n$		X		
	C-11	Carbon-11	(20 min)	$^{14}_7\text{N} + p \rightarrow ^{11}_6\text{C} + \alpha$	PET			
	Cu-67	Copper-67	(61,9 hr)	$^{68}_{30}\text{Zn} + p \rightarrow ^{67}_{29}\text{Cu} + 2p$		X		
	F-18	Fluorine-18	(110 min)	$^{18}_8\text{O} + p \rightarrow ^{18}_9\text{F} + n$ $^{20}_{10}\text{Ne} + ^2_1\text{D} \rightarrow ^{18}_9\text{F} + \alpha$	PET			
	Ga-67	Gallium-67	(3,3 d)	$^{68}_{30}\text{Zn} + p \rightarrow ^{67}_{31}\text{Ga} + 2n$ $^{67}_{30}\text{Zn} + p \rightarrow ^{67}_{31}\text{Ga} + n$	SPECT			
	Ge-68	Germanium-68	(270 d)	$^{69}_{31}\text{Ga} + p \rightarrow ^{68}_{32}\text{Ge} + n$			X	Ga-68
	I-123	Iodine-123	(13 hr)	$^{121}_{51}\text{Sb} + \alpha \rightarrow ^{123}_{53}\text{I} + 2n$ $^{124}_{54}\text{Xe} + p \rightarrow ^{123}_{53}\text{I} + 2n + 2e^-$ $^{122}_{52}\text{Te} + \alpha \rightarrow (^{123}_{54}\text{Xe} + 3n) \rightarrow ^{123}_{53}\text{I}$ $^{122}_{52}\text{Te} + ^2_1\text{D} \rightarrow ^{123}_{53}\text{I} + n$	SPECT			
	I-124	Iodine-124	(4,18 d)	$^{124}_{52}\text{Te} + p \rightarrow ^{124}_{53}\text{I} + n$ $^{124}_{52}\text{Te} + ^2_1\text{D} \rightarrow ^{124}_{53}\text{I} + 2n$	PET			
	In-111	Indium-111	(2,8 d)	$^{112}_{48}\text{Cd} + p \rightarrow ^{111}_{49}\text{In} + 2n$ $^{109}_{47}\text{Ag} + \alpha \rightarrow ^{111}_{49}\text{In} + 2n$	SPECT	X		
	N-13	Nitrogen-13	(10 min)	$^{16}_8\text{O} + p \rightarrow ^{13}_7\text{N} + \alpha$	PET			
	Na-24	Sodium-24	(15 hr)	$^{27}_{13}\text{Al} + ^2_1\text{D} \rightarrow ^{24}_{11}\text{Na} + \alpha + p$	SPECT			
	O-15	Oxygen-15	(2 min)	$^{15}_7\text{N} + p \rightarrow ^{15}_8\text{O} + n$ $^{14}_7\text{N} + ^2_1\text{D} \rightarrow ^{15}_8\text{O} + n$	PET			
	Sr-82	Strontium-82	(25 d)	$^{82}_{38}\text{Rb} + p \rightarrow ^{82}_{38}\text{Sr} + Xn$			X	Rb-82
	Tc-89m	Technetium-89m	(6 hr)	$^{100}_{42}\text{Mo} + p \rightarrow ^{99m}_{43}\text{Tc} + 2n$	SPECT			
	Tl-201	Thallium-201	(73 hr)	$^{203}_{81}\text{Tl} + p \rightarrow ^{201}_{82}\text{Pb} + 3n \rightarrow ^{201}_{81}\text{Tl} + e^+$	SPECT			
	Zr-89	Zirconium-89	(78,4 hr)	$^{89}_{40}\text{Y} + p \rightarrow ^{89}_{40}\text{Zr} + n$	PET			
Production via reactor	Ac-225	Actinium-225	(10 d)	$^{226}_{88}\text{Ra} + p \rightarrow ^{225}_{89}\text{Ac} + 2n$		X		
	Ho-166	Holmium-166	(26 hr)	$^{165}_{67}\text{Ho} + n \rightarrow ^{166}_{67}\text{Ho}$		X		
	I-125	Iodine-125	(60 d)	$^{124}_{54}\text{Xe} + n \rightarrow ^{125}_{54}\text{Xe} \rightarrow ^{125}_{53}\text{I} + e^+$	SPECT	X		
	I-131	Iodine-131	(8 d)	$^{130}_{52}\text{Te} + n \rightarrow ^{131}_{52}\text{Te} \rightarrow ^{131}_{53}\text{I} + e^-$	SPECT	X		
	Ir-192	Iridium-192	(74 d)	$^{191}_{77}\text{Ir} + n \rightarrow ^{192}_{77}\text{Ir}$		X		
	Lu-177	Lutetium-177	(6,65 d)	$^{176}_{71}\text{Lu} + n \rightarrow ^{177}_{71}\text{Lu}$ $^{177}_{70}\text{Yb} \rightarrow ^{177}_{71}\text{Lu} + e^-$	SPECT	X		
	Mo-99	Molybdenum-99	(66 h)	$^{235}_{92}\text{U} + n \rightarrow ^{236}_{92}\text{U}^* \rightarrow ^{99}_{42}\text{Mo} + n + X$ or neutron capture of molybdenum-98 (Mo-98)			X	Tc-99m
	Pb-212	Lead-212	(10,6 h)	Decay of Ra-224 (obtained by decay of Th-228)		X		
	Ra-223	Radium-223	(11,4 d)	$^{226}_{88}\text{Ra} + n \rightarrow ^{227}_{88}\text{Ra} \rightarrow ^{227}_{89}\text{Ac} \rightarrow ^{223}_{88}\text{Ra}$		X		
	Re-186	Rhenium-186	(3,8 d)	$^{185}_{75}\text{Re} + n \rightarrow ^{186}_{75}\text{Re}$	SPECT	X		
	Re-188	Rhenium-188	(17 h)	$^{187}_{75}\text{Re} + n \rightarrow ^{188}_{75}\text{Re}$		X		
	Se-75	Selenium-75	(120 d)	$^{74}_{34}\text{Se} + n \rightarrow ^{75}_{34}\text{Se}$		X		
	Sm-153	Samarium-153	(47 h)	$^{152}_{62}\text{Sm} + n \rightarrow ^{153}_{62}\text{Sm}$	SPECT			
	Sr-89	Strontium-89	(50 d)	$^{88}_{38}\text{Sr} + n \rightarrow ^{89}_{38}\text{Sr}$ $^{89}_{39}\text{Y} + n \rightarrow ^{89}_{38}\text{Sr} + p$		X		
	Tb-161	Terbium 161	(6,9 d)	$^{160}_{64}\text{Gd} + n \rightarrow ^{161}_{64}\text{Gd} \rightarrow ^{161}_{65}\text{Tb} + e^-$		X		
	Y-90	Yttrium-90	(64 h)	$^{89}_{39}\text{Y} + n \rightarrow ^{90}_{39}\text{Y}$ $^{90}_{40}\text{Zr} + n \rightarrow ^{90}_{39}\text{Y} + p$		X		

Table 35 : Nuclear reaction and production process for Health-used radioisotopes

The typical supply chain of Tc-99m through Research Reactors is detailed in the next chapters, alternatives supply chains are currently studied (mainly in North America). A focus is also performed on these alternatives technologies. An alternative way to produce Tc-99m could lie in cyclotrons (e.g. *Canada is investigating this possibility*), but many issues need to be resolved to enable an industrial production of Tc-99m (higher production costs, Tc-99m impurity, Cyclotron Installed Base...). A comparison is performed in the next chapters between the different Tc-99m supply chains and the limits of the Cyclotron path.

A12. Economic assessment of Tc-99m supply chain with Research Reactors

A.12.1. The Tc-99m supply chain

For SPECT exams, Tc-99m currently represents the most-used radioisotopes, with a very specific supply chain, based on Research Reactor production. The current Tc-99m supply chain can be briefly summarized as below:



Figure 95: Tc-99m supply chain - Source
http://www2.mallinckrodt.com/nuclear_imaging/global_mo-99_supply_chain.aspx

(1) U 235 Targets	Molybdenum 99 (Mo-99) is produced in nuclear reactors utilizing either Highly Enriched Uranium 235 (HEU) or Low Enriched Uranium 235 (LEU) targets. These targets, either tubular or flat and of varying size, are fabricated as small from HEU or LEU and aluminium designed specifically for each reactor.
(2) Reactor Facility	HEU or LEU targets are placed in or near the core of the reactor. The location within the reactor allows high neutron thermal fluxes (typically $> 10^{14}$ n/cm ² /s) to surround the HEU / LEU. Fission reactions occur, resulting in production of Mo-99 and a number of other fission products.
(3) Mo-99 Facility	After approximately six days in the reactor, fission produced Mo-99 has reached an optimum level. The targets are then removed and transferred to a Mo-99 processing facility where the targets are dissolved and chemically separated. Mo-99 facilities can only accept HEU / LEU targets from specific reactors for various reasons, including geographic location (proximity to the reactor), required technical specifications and regulatory authority approval. The finished product raw material Mo-99 is then isolated as radiochemical and shipped to the next stage in the process.
(4) Generator Facility	The radiochemical Mo-99 is transferred to a manufacturing facility in specialized transport containers via various overnight or same day shipping arrangements so it can be used to manufacture Mo-99/ Tc-99m generators. Generator manufacturing is a health authority approved complex multistep process obeying to GMP (good manufacturing practices). Finished product generators must meet all approved specifications, as spelled out by the manufacturer's registered drug application, as filed with the appropriate governing regulatory agency.
(5) Pharmacies Hospitals	Generators that meet the specific quality release criteria will move on to the distribution channel. Any of a variety of transportation methods may be necessary including air, ground, or a combination depending on customer location. The generators are then shipped for same or next day delivery to hospitals and radiopharmacies for elution and used to make diagnostic radiopharmaceuticals.

Generator production follows a schedule where time is of essence, due to radioactive decay of Mo-99, from the moment when the U235 targets are removed from the Research Reactor core. The different steps duration of Mo-99 supply chain will differ from one producer to another, thus it is inconsistent to compare generator Mo-99 activity based on "not-fixed" milestones: e.g. comparing two manufacturer's generator activity

based on End of Processing activity won't make sense, generator manufacturing and transport will differ from one product to another. In order to make things comparable, radiopharmacists use the independent notion of "calibration date 6 days post-delivery" (as explained hereafter). Based on standard decay tables, they easily estimate the generator activity day after day.

Some definitions of milestones used in the Tc-99m supply chain

End of Bombardment (EOB): Activity at the end of the irradiation
End of Processing (EOP): Activity at the end of the processing activities
End of Calibration: Activity measured of the Generator inside the Generator Manufacturing Plant and used as a reference by Radio pharmacists to calculate Elution and doses
6-day Ci EOP: Activity measured in the Generator 6 days after the end of Processing
Calibration "date of delivery": Activity corresponds to the activity in the Generator after calibration at the generator facility.
Calibration 6 days post-delivery: Activity corresponds to the activity remaining in the generator 6 days after delivery, it is the definition mainly used by vendors and in the European Union.

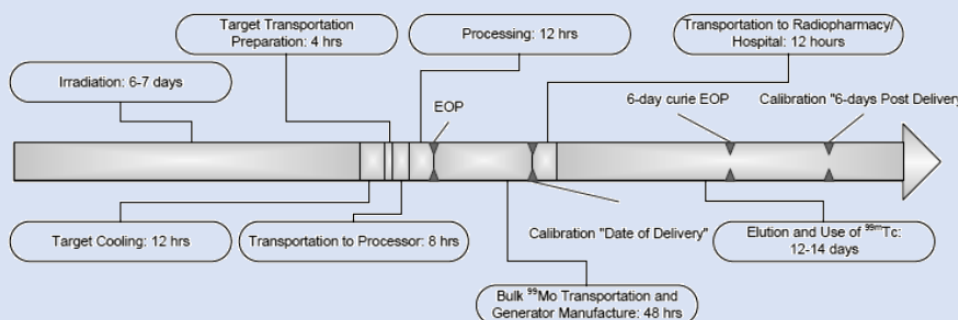


Figure 96: Typical timeline of Tc-99m supply chain - OECD/NEA

These different milestones are used by industrial actors to quantify the Mo-99/Tc-99m Activity sold to the next link of Tc-99m supply chain (for example, the End of Processing (EOP) physical parameter is used between Processors and Generator Manufacturers to quantify the Mo-99 activity sold by Processors).

For the final user (radiopharmacist) it is necessary to dispose of a physical parameter that estimates the Tc-99m activity harvestable. Depending on the country and the generator manufacturer, different definitions are used: the "calibration date of delivery" or "calibration 6 days post-delivery".

On one side, the activity is the one measured in the generator at the manufacturer facility and radiopharmacists will have to use decay formulas to estimate the activity actually received after delivery; while the second approach gives the activity after 6 days in the hospital, decay factor is then used backward to estimate the activity on the days preceding this date.

Example – IBA TEKCIS10GBq

Manufactured on Day 0, Received on a Day 1& Calibrated for Day 7

Day 0 Saturday	Day 1 Sunday	Day 2 Monday	Day 3 Tuesday	Day 4 Wednesday	Day 5 Thursday	Day 6 Friday	Day 7 Saturday
60.87 GBq	47.31 GBq	36.76 GBq	28.58 GBq	22.22 GBq	17.26 GBq	13.42 GBq	10.43 GBq

* Figures in the table corresponds to the minimum activity of Tc-99m in GBq harvestable from the Generator at 8:00 on the basis of a single elution per day

A.12.2. Generator Cost Evaluation

Current Mo-99/Tc-99m generators prices were collected through Inami (Belgium National Social Security Institute), Belgium currently being the only country in EU that directly reimburses the radiopharmaceuticals, where other countries base their reimbursements on exam global cost (per-case reimbursement). Inami publishes on a monthly-basis Tc-99m dose reimbursement, along with generators prices³⁰⁵ as illustrated in the next figure.

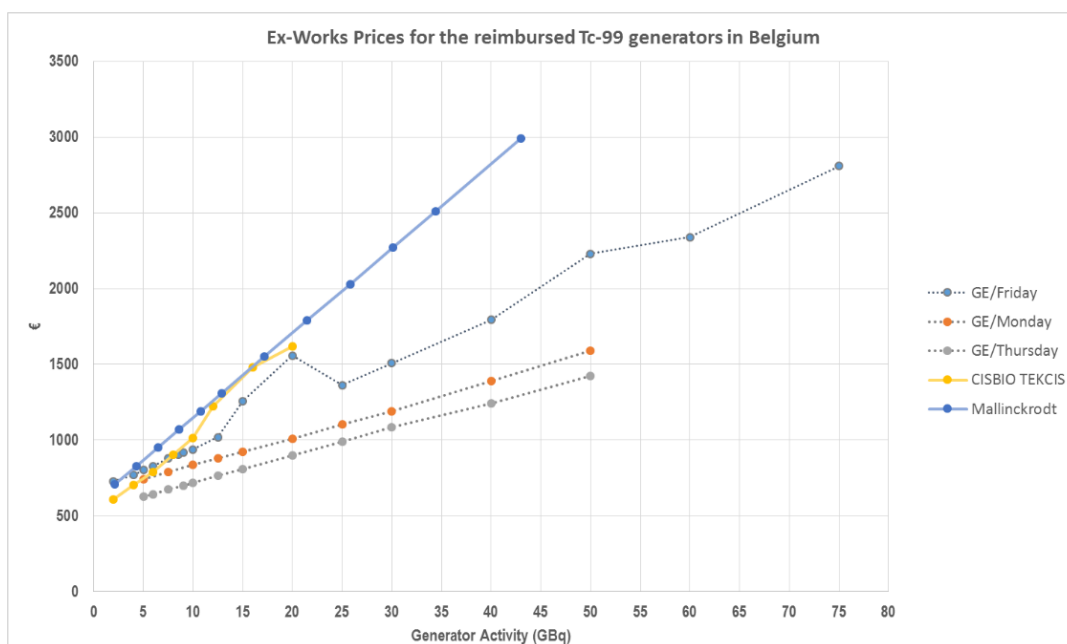


Figure 97: Drytec (GE), TEKIS (CISBIO) and ULTRATECHNEKOW FM (Mallinckrodt) generator prices for the different Typical Generators used in Belgium – Source: INAMI Radiopharmaceuticals reimbursement database

OECD NEA³⁰⁶ estimated in 2010 the selling price breakdown of a six-day curie EOP of Molybdenum-99, with standard manufacturing process using reactor irradiation. Tc-99m generators selling price evaluation range was 400-610€ per 6 day-Ci of Mo-99 End of Processing for HEU and 530-790€ for LEU.

Final generator price in 6-day curie EOP of Mo-99 (OECD/NEA)			
	Costs at irradiation stage	Cost at processor stage	Generator price (6-day curies EOP)
HEU Targets	USD 120 to 175	USD 380 to 670	USD 555 to 850
in € ₂₀₁₀	-	-	€ 400 to 610
LEU Targets	USD 300 to 430	USD 560 to 930	USD 735 to 1 100
in € ₂₀₁₀	-	-	€ 530 to 790

Table 36 : Generator prices issued from HEU/LEU targets

According to experts surveyed³⁰⁷, Mo-99/Tc-99m prices increased over the last decade, thus OECD/NEA findings can be reassessed based on generators prices collected.

³⁰⁵ Radiopharmaceuticals reimbursement database updated on 1st of April 2017

http://www.inami.fgov.be/SiteCollectionDocuments/list_radiopharmaca_20170401.pdf

³⁰⁶ The Supply of Medical Radioisotopes - Review of Potential Molybdenum-99/ Technetium-99m Production Technologies 2010

³⁰⁷ Guy Turquet de Beauregard Interview – Former AIPES President

In order to evaluate Generator Prices expressed in 6-day Ci EOP, OECD/NEA made several hypotheses on the duration of the different steps of the supply chain (*processed Mo-99 delivery, generator manufacturing duration, radiopharmacists delivery...*), these durations are not standardized and shows important variations between players (*Mo-99 is not necessarily supplied to generator manufacturer on a daily basis, generators are produced only on some days of the weeks, delivery time varies from a few hours to days...*). Thus, converting calibration date Ci to 6-day Ci EOP is extremely theoretical.

For those generators that were calibrated at six days from the date of delivery, the conversion factor represents the difference between the ⁹⁹Mo available six days post EOP and that available eight days post EOP. There is approximately 1.656 curies of ⁹⁹Mo on six days EOP compared to a curie eight days EOP. Therefore, the price per six-day Ci is found by:

$$(\text{Price/calibrated Ci})/1.655840548 = \text{price/six-day curie EOP}$$

Figure 98: 6-day calibration Ci conversion formula to 6day Ci EOP - The Supply of Medical Radioisotopes An Economic Study of the Molybdenum-99 Supply Chain OECD/NEA 2010

For sole comparison purpose with OECD/NEA results, the study methodology has been used to assess current Mo-99 prices:

Generator Activity Calibration 6-day post delivery	Generator Price Friday calibration date	Price per Ci Calibration 6-day post delivery	Price per 6day Ci EOP (using OECD/NEA conversion factor)
Drytec 10 GBq	939€	3474€/Calibrated Ci	2098€₂₀₁₇/6day Ci EOP
Drytec 30 GBq	1509€	1861€/Calibrated Ci	1123€₂₀₁₇/6day Ci EOP
Drytec 60 GBq	2339€	1442€/Calibrated Ci	870€₂₀₁₇/6day Ci EOP

Mo-99 cost per 6-day Ci EOP presents large variations, because of the diversity of generators used in the world³⁰⁸ (from 2 to 75 GBq); the relation between Mo-99 activity and generator price not being proportional.

Calculations illustrate the overall increase of generators market prices over the last decade, the following chapter compare the cost of Tc-99m dose injected to patients, from Mo-99 generators and cyclotrons. Despite Mo-99 cost increase, we shall observe that cyclotron approach remains more expensive.

³⁰⁸European Market mainly relies on low activity generators 6-15 GBq (Calibration 6-days post-delivery), because of the presence of radiopharmacies directly inside hospitals, where American market is based on centralized radiopharmacies preparing doses for multiple hospitals.

A.12.3. Tc-99m dose cost evaluation

In order to compare the cost efficiencies of Tc-99m production through research reactors (generators) and cyclotrons (direct Tc-99m manufacturing), the quantity of Tc-99m that can be harvested per generator has to be estimated, along with its potential daily use.

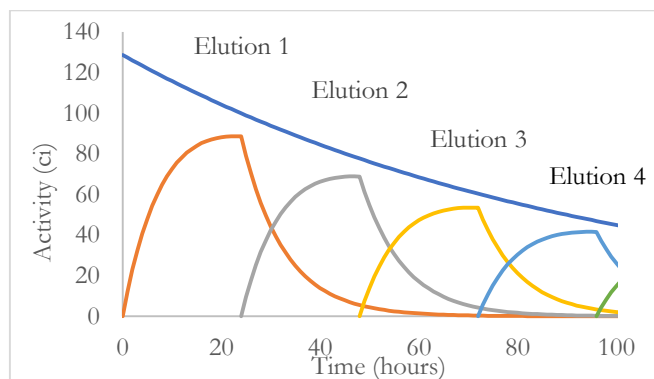


Figure 99: Elution Process for the first few days of generator utilisation

This quantity depends first upon the way the generator is used, i.e. the number of elutions per day. On the basis of interviews, we considered that a radiopharmacist will typically perform elution on a regular basis 5 day a week, 1 time a day (at 8 AM)³⁰⁹, as illustrated by the figure above.

Calculations shows that with a Mo-99 initial activity (i.e. activity of Mo-99 at the date of the first elution, considered here on a Monday) of 100_{base 100}, the cumulative available Tc-99m activity that can be eluted during say 21 days of utilization is ~340_{base 100} (i.e. Tc-99m cumulative activity harvested at the elution). Given a typical elution factor³¹⁰ of Mo-99/Tc-99m generator of 0,9, the cumulative activity of Tc-99m eluted during generator use is roughly ~310_{base 100}.

Elution	Time (hr)	A (Mo)	A (Tc)
	0	128,7	0,0
Monday	24	100,0	88,6
Tuesday	48	77,7	68,9
Wednesday	72	60,4	53,5
Thursday	96	46,9	41,6
Friday	120	36,5	32,3
Week end	144	28,3	25,1
	168	22,0	19,5
Monday	192	17,1	15,2
Tuesday	216	13,3	11,8
Wednesday	240	10,3	9,2
Thursday	264	8,0	7,1
Friday	288	6,2	5,5
Week end	312	4,8	4,3
	336	3,8	3,3
Monday	360	2,9	2,6
Tuesday	384	2,3	2,0
Wednesday	408	1,8	1,6
Thursday	432	1,4	1,2
Friday	456	1,1	0,9
Week end	312	4,8	0,7
	336	3,8	3,3

Figure 100: Typical Mo-99 and Tc-99m activity inside generator

³⁰⁹ Another approach to maximize generator use is to perform two elutions per day. For practical reasons hospitals don't systematically optimize to that extent their generator use, and only perform one elution per day. Calculations show that two elutions per day enable a net daily gain (+40%) of the Tc-99m activity, but increase radiopharmacists preparation time.

³¹⁰ A minimum elution factor of 0,9 is used by GE in Drytec generators documentation

In practice, generators are rarely used during more than one week, Mo-99 decay makes generator much more difficult to use³¹¹ after 9 days, 90% on the initial activity being lost. For the next calculations, we will assume that in period of no-shortage, radiopharmacists do not try to optimize Tc-99m use to its maximum and simplify their procurement; thus, generators are only used for a duration of 7 days and replaced by a new one.

In order to dispose of a stable quantity of Tc-99m during a week, radiopharmacists use different generators in parallel, here, we will assume that a first generator is delivered on the Monday and a second one on Wednesday (with lesser Mo-99 activity), generators capacity are considered compatible with hospital utilization (detailed in next paragraph).

Exam	time since elution (min)	A Tc initial necessary (MBq)
1	30,0	741,6
2	83,3	821,7
3	136,7	910,4
4	190,0	1008,8
5	243,3	1117,8
6	296,7	1238,5
7	350,0	1372,3
8	403,3	1520,5
9	456,7	1684,7
total A(Tc) initial		10416,2

Figure 101: Daily need of Tc-99m per gamma camera for SPECT exams with one elution per generator per day

Quantity of Tc-99m necessary per clinical indication

Injected dose to the patients varies from one SPECT exam to another, depending on patient characteristics (weight, age...) and the organ/system to be investigated (*bone ~ 600 MBq, myocardial perfusion ~ 600 MBq, brain ~ 800 MBq, white cells ~185 MBq...*), an average dose of 700 MBq (~20 mCi) is often used in the literature as a median dose for SPECT exams³¹².

Imaging Equipment are operated within the medical centres opening hours (8h-17h). Discrepancies exist between public and private institutions in terms of equipment utilization rate³¹³. Planning optimization for private hospitals are easier (same SPECT exams could be regrouped on a single day, less emergencies examinations...). We will consider that a typical SPECT Equipment (in a public hospital) can perform 9 exams per day based on these opening hours.

	Activity G1 (GBq)	G2	Total	Loss
Lundi	8,13	29,4	37,53	17
Mardi	6,32	22,8	29,12	8
Mercredi	28,7	17,7	46,4	26
Jeudi	22,3	13,8	36,1	15
Vendredi	17,3	10,7	28	7
			177,15	73,0

Figure 102: Daily Tc-99m production with two generators

³¹¹Tc-99m concentration in eluted solution is very low after 9 days (~10% of Tc99 concentration in first elution), while radiopharmacists also have requirements on the Tc-99m concentration. Thus, generators are often used only during one week.

³¹² In addition to this "nominal" required activity, Tc-99m concentration must be within acceptable range, thus it can lead to stop using the generator because of the rather low concentration of Tc-99m in the last days of utilization.

³¹³ IRSN (France) statistics on Imaging Use

With such hypothesis, a gamma camera needs to be used with a generator whose daily elution is more than 10 500 MBq of Tc-99m. For example, for a typical Nuclear Medicine service operating 2 gamma cameras, daily elution needs are in the range of 21 000 MBq of Tc-99m. Such needs can be satisfied through the use of a 8 GBq Generator (received on Monday and calibrated on the following Saturday) and a 6 GBq generator (received on Wednesday and calibrated on next Wednesday). Based on these assumptions, typical price range of a Tc-99m dose can be evaluated.

Parameter	Value
Weekly Generator Cost ³¹⁴	
8 GBq (example: TEKCIS – CisBio)	905 €
6 GBq (example: Drytec – GE)	830 €
SPECT examinations per week (i.e. number of Dose of Tc-99m prepared)	90 exams
Tc-99m average dose cost	19 €/dose

Table 37 : Tc-99m dose cost evaluation

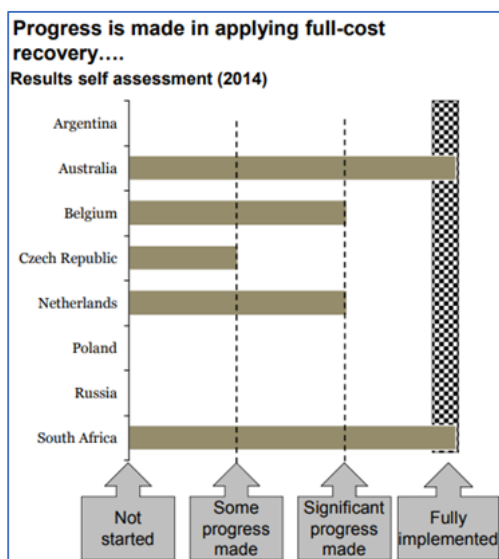
This typical dose price could be slightly reduced through bi-daily elutions, extension of generator utilization, patients planning optimization (i.e. increasing the number of examinations per day). Being able to perform 2 additional exams per day, with the same generators would lead to a Tc-99m average dose cost of 15.7€/dose.

As a conclusion, it appears that Tc-99m produced through Mo-99 generators offers a flexible and affordable supply solution for SPECT exams. The centralized production in Research Reactors, despite the series of intermediate players (processors, generators manufacturers...) delivers "low cost Tc-99m (<20€/dose)" due to large scale production savings. A large potential of optimization of the generator use may exist, usable in periods of shortages.

³¹⁴ INAMI database

A.12.4. Full Cost Recovery Issue

A specificity of the Mo-99 generators market is the partial lack of Full Cost Recovery at certain steps of the supply chain, especially for the irradiation in research reactors. These installations are used for many applications (targets irradiation, nuclear programmes support...), thus for many installations Mo-99 production is not the core “business” of the installation and large public funding has historically been used to cover construction and O&M costs, biasing the global Mo-99 market (see namely the Canadian NRU story). Following the OECD/NEA HLG and the European Observatory initiatives, Full Cost Recovery efforts have been engaged, as shown on the illustration below.



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

Figure 103: PwC vision of progress towards full cost recovery for Research Reactors

Even if the above figure may be discussed, it shows that as of today, full cost recovery is not yet implemented everywhere despite calculations indicating that full cost recovery would only induce a very limited increase on Tc-99m procedure cost (<1%³¹⁵) as shown below. The problem at stake is the upwards pass-through of prices increases at the end of the supply chain. This difficult pass-through is due to the market structure. Hence efforts must be pursued.

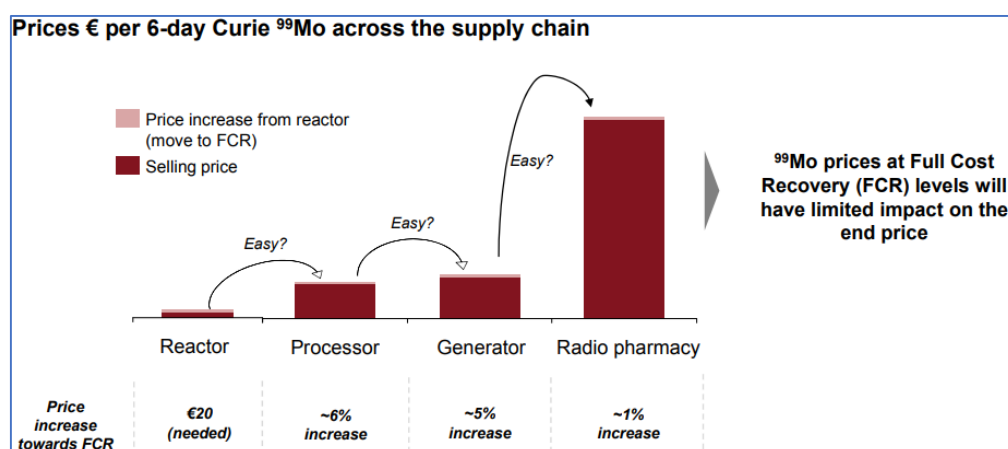


Figure 104 : Limited impact of FCR on final examination costs (PwC)

³¹⁵ The Supply of Medical Isotopes: an economic study of Molybdenum-99 supply chain, OECD (2010)

A.12.5. Economic assessment of Tc-99m production through Cyclotrons

The fast development of PET Scan procedures in the last decade highly impacted the cyclotron market. In order to dispose of the radiopharmaceuticals needed for the exams (F-18-FDG, C-11, N-13...), with very short half-life, cyclotrons were installed in many hospitals and medical centres for an onsite production. In 2014, there were more than 950 medical cyclotrons in the world³¹⁶, with roughly 450 cyclotrons operating between 16-19 MeV, and 100-300 μ A. Cyclotrons are now widely available over the world, improving their utilisation range through the production of Mo-99 and/or Tc-99m is a scenario currently assessed by different countries.

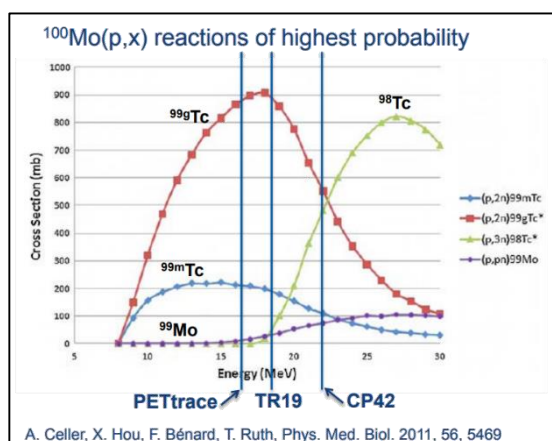


Figure 105: $^{100}\text{Mo}(p,x)$ reactions of highest probability

A beam of energetic protons from a cyclotron (about 20 MeV) can be used to produce Tc-99m via the bombardment of a molybdenum target highly enriched in Mo-100 (> 99%). Direct production of Tc-99m in a Cyclotron is highly dependent on the characteristics of the cyclotron used for the irradiation (cyclotron energy, irradiation duration, particle flux intensity...), the optimal energy range being 16-22 MeV.

Several experiments and theoretical researches were performed in the last few years to demonstrate the feasibility of Tc-99m direct production, as summarized in the table on next page.

Although absolute production yields of Tc-99m are higher at 19 or 24 MeV, the analysis of ratios of Tc-99m to other reaction products indicate that proton energies of 16-19 MeV may be the most advantageous energy region, where the Tc-99m is high while the number of contaminants is minimized. Experiments (cf. table below) showed that Tc-99m can be produced in cyclotrons, and then used in diagnostic examinations similarly to Tc-99m produced through Mo-99/Tc-99m generators. Nevertheless, impurities issues are still present, either in terms of additional dose to the patient (*recent clinical tests showed*

³¹⁶ Direct Production of ^{99m}Tc via $^{100}\text{Mo}(p,2n)$ on Small Medical Cyclotrons - P. Schaffer, F. Bénard, A. Bernstein, K. Buckley, A. Celler, N. Cockburn

up to 10% dose increase due to Tc-99m impurities³¹⁷), or imaging quality (with higher ⁹⁴⁻⁹⁷Mo contents, image quality is degraded³¹⁸).

Status	Equipment	Yield	Duration	Intensity	Source
Experiment	IBA Cyclone GE PETtrace	2 Ci	3 hours	100 µA	[1]
Experiment	25 MeV Cyclotron	2.75 Ci	-	160 µA	[2]
Experiment	TR 24 MeV Cyclotron	8.4 Ci	4 hours	250 µA	[3]
Experiment	TR 24 MeV Cyclotron	12.4 Ci	8 hours	250 µA	
Experiment	GE PETtrace 16,5 MeV	4.7Ci	6 hours	130 µA	[4]
Experiment	ACSI TR19 18MeV	9.4Ci	6 hours	240 µA	
Experiment	ACSI TR30 24MeV	34Ci	6 hours	450 µA	

Table 38 : Published experiments of Tc-99m production with cyclotrons³¹⁹

Cost evaluation of Tc-99m direct production will be assessed through two scenarios:

- #1: Production using a typical cyclotron installed capacity (i.e. 15-20 MeV with 100 µA current), that produce Tc-99m every day for internal use in an hospital (cyclotron dedicated to a hospital)
- #1': Production using standard cyclotrons, dedicated to Tc-99m production through specific enhancements (16 MeV with 130 µA current), production for several hospitals.
- #2: Production using larger cyclotrons (i.e. 24 MeV with 450 µA current) for several hospitals.

Those examples are based on Triumf experiments³²⁰, in each case a Tc-99m batch has been produced in Triumf cyclotrons with the associated parameters.

Parameters	#1	#1'	#2
Beam Energy	16 MeV	16 MeV	24 MeV
Current	100 µA	130 µA	450 µA
Irradiation Duration	3 hours	6 hours	6 hours
Tc-99m Production yield	2 Ci	4.7 Ci 5 Ci (theoretical)	34 Ci 40 Ci (theoretical)
Production days per year	260	260	260
Mo100 Targets needed per year	260	260	260
Cyclotron lifetime	30 years ³²¹	30 years	30 years

³¹⁷Radioisotopic Purity of Sodium Pertechnetate 99mTc Produced with a Medium-Energy Cyclotron: Implications for Internal Radiation Dose, Image Quality, and Release Specifications.

<https://www.ncbi.nlm.nih.gov/pubmed/26205300>

³¹⁸ The impact of impurities in cyclotron-produced 99mTc on image quality

http://jnm.snmjournals.org/content/57/supplement_2/1873?trendmd-shared=0&related-urls=yes&legid=jnumed;57/supplement_2/1873

³¹⁹ [1] - TECHN-Osp R&D activities aimed at an industrially-based technology for future homeland accelerator-Tc-99m production based on a selected cyclotrons' network in Italy

[2] Cyclotron production of technetium radionuclides using a natural metallic molybdenum thick target and consequent preparation of [Tc]-BRIDA as a radio-labelled kit sample Hossain Targholizadeh, Gholamreza Raisali, Amir R. Jalilian, Nima Rostampour, Mohammadreza Ensaf, Mohsen K. Dehghan

[3] - Cyclotron produced Tc-99m on a TR24 high current target station, Katherine Gagnon, John Wilson, Brent Thomas, Joseph Romaniuk, Jan Andersson, Jonathan Doupe, Steve McQuarrie and Alexander McEwan

[4] Tc-99m Production Development at TRIUMF - Paul Schaffer

https://indico.cern.ch/event/366464/contributions/1782255/attachments/728653/999809/20150326_Schaffer-TRIUMF_Consortium_-_EUCard_-_v3.pdf

³²⁰ 99mTc Production Development at TRIUMF - Paul Schaffer

³²¹ §5 <https://www.isotopes.gov/outreach/reports/Cyclotron.pdf>

Parameters	#1	#1'	#2
Yearly Tc-99m gross production	520 Ci	1222 Ci	8840 Ci
Target dissolution and Tc-99m purification process duration...	90 min	90 min	90 min
... and yield	93%	93%	93%
Yearly Tc-99m net production (time and yield losses ~ 22%)	~407 Ci	~ 956 Ci	~ 6919 Ci
Usable Tc-99m for Hospital (3hrs transportation losses ~29%)	~407 Ci (prod. in hospital)	~ 678 Ci (3hrs transport)	~ 4912 Ci (4hrs transport ³²²)

Table 39: Triumf experiments performances data

The CAPEX and OPEX used to evaluate the production costs are the following:

Parameters	#1	#1'	#2
Cyclotron Cost	8 M€	8 M€	12 M€
Facility Cost	3 M€	3 M€	10 M€
Processing Installations	400 k€	400k€	400k€
Operation and Maintenance Costs	300 k€/year	300k€/year ³²³	750 k€/year
Mo-100 Supply Cost (>95 % Mo-100)	500-2700€/g ³²⁴	500-2700€/g	500-2700€/g
Mo-100 qty per target	1-1,5g ³²⁵	1-1,5g	1-1,5g
Target Manufacturing Total Cost ³²⁶	1000 €/target	1000 €/target	1000 €/target
Loss of Mo-100 during retreatment	10%	10%	10%
Target total cost with retreatment*	550 €/target	550 €/target	550 €/target
Yearly Target Cost	143 k€	143 k€	143 k€

Table 40 : CAPEX & OPEX used in our calculations

With all these elements, the dose cost can be computed:

Parameters	#1	#1'	#2
Capital Cost	11,4 M€	11,4 M€	22,4 M€
O&M (yearly)	443 k€/year	443 k€/year	893 k€/year
D&D Cost ³²⁷	300-500k€	300-500k€	300-500k€
Tc-99m average prod. Cost/yr **	4065 €/Ci	2440 €/Ci	666 €/Ci
Tc-99m average annual prod. Cost	1,654 M€	1,654 M€	3,271 M€
Usable Tc-99m for Hospital per year	407 Ci	~ 678 Ci	~ 4912 Ci
Usable Tc-99m for Hospital per day	1,56 Ci	2,60 Ci	18,89 Ci
Average Tc-99m daily needs for a γ-camera performing 9 exams	11 GBq ~ 0,3 Ci		
Cyclotron production enough to satisfy...	1 hospital 2 γ-cameras 18	4 hospitals 8 γ-cameras 72	31 hospitals 62 γ-cameras 558

³²² Canadian average hypothesis for dose delivery, http://www.cbc.ca/polopoly_fs/1.3146825.1436558160!/fileImage/httpImage/image.jpg_gen/derivatives/origin_al_940/potential-isotope-production-locations.jpg

³²³ TR-24 Cyclotron Economics <http://www.advancedcyclotron.com/cyclotron-solutions/tr24>

³²⁴ New precipitation method for isolation of 99mTc from irradiated 100Mo target

³²⁵ http://Mo-99.ne.anl.gov/2015/pdfs/presentations/S8P4_Buckley_Presentation.pdf

³²⁶ Manufacturing cost of Mo-100 target is assumed to be roughly equivalent to Mo-100 procurement cost, with 1g of Mo-100 at 500€/g according to paper: Production of 100Mo for Cyclotron conversion to 99mTc - H.J. Strydom, E. Ronander, J. Viljoen, G. Kemp, J.J. Grant, P.E. Uys, and B.D. Esterhuyse

³²⁷ Feasibility study on the DFP adoption of medical cyclotron decommissioning in the Republic of Korea - Rina Woo

	doses/day 4680 doses/yr	doses/day 18720 doses/yr	doses/day 145080 doses/yr
<i>Production direct loss (i.e production not sold)</i>	0,96 Ci	0,2 Ci	0,2 Ci
Tc-99m average dose cost	350€/dose	89€/dose	22,5€/dose

* Retreatment of Mo-100 targets has an efficiency of 90%, it means that with 100 targets, it is possible to prepare 90 targets, then 81... In the end 1000 targets can be prepared with an initial Mo-100 quantity of 100 targets.

** Discount Rate 10%

Table 41: Cyclotron produced Tc-99m Dose cost

The development of Tc-99m production in cyclotron largely relies on new cyclotron generation with higher flux intensity (in the range of 500 μ A), enabling large scale production with reduced costs. Canada is progressing with Tc-99m cyclotron production, clinical applications have been performed and New Drug Submission (NDS) to the authorities is under study.

Cost-competitiveness of Tc-99m Cyclotron production versus reactor production current costs seems hardly achievable, as demonstrated by previous calculations (*due to important radioactive decay of Tc-99m and physical constraint on Cyclotron Intensity*).

Others remaining challenges are currently addressed by cyclotron specialists to enable a large-scale production of Tc-99m with cyclotrons.

A.12.6. Cyclotrons & generator-based Tc-99m comparison

The following table summarize the different findings

	Strengths	Weaknesses ³²⁸
Tc-99m Generators produced with Research Reactors	GMP: Reactor supply chain is now fully mastered and reliable, with proven GMP more than 50years old Economic: Low production cost of Tc-99m Centralized Worldwide Production Ease of use: Tc-99m generators enable a convenient/comfortable supply management at the radiopharmacist level (one delivery per week/2weeks, easy to use, no need to optimize procedures planning) Versatility: Research reactors can easily be used simultaneously for various purposes (others than RI production) and today also produce the RI needed for therapy or sealed sources	Availability: Mo-99 shortages were due to unexpected reactor shutdown, with sometimes long outages for repair Radioactive Wastes and Spent Fuel Research Reactors produce a larger quantity of wastes (including HLW) than cyclotrons
Tc-99m Cyclotron Production	Supply chain simplification: less actors involved in Tc-99m supply chain, and local production capacity becomes possible for low investment cost Single tool: cyclotrons theoretically able to produce SPECT imaging isotopes (Tc-99m) and PET imaging isotopes (F-18). But daily yields ? Less radioactive waste	Economic: Higher production cost compared to research reactors Quality Control: Decentralized production leads to a greater likelihood of product variability, dose uncertainty; Regulatory: Considerations need to include target isotopic enrichment, but also batch-to-batch target consistency, irradiation energy/duration, etc. Availability: a viable alternative/backup equipment to be used in case of unexpected outage ? Equipment development: industry has to prove that current cyclotron can be modified to enable large scale production of Tc-99m

Table 42: Synthesis of the comparison of reactor and cyclotrons for Tc-99m production

³²⁸ These challenges are coming from TRIUMF publication (20150326_Schaffer-TRIUMF-Consortium_-_EUCard_-_v3)

A13. The Mo-99/Tc-99m supply and demand

In the following chapter we delve deeper into the situation concerning the supply chain, critical suppliers of and demand for Molybdenum/Technetium in the medical realm. We explain the construction of a computer simulation model that feeds into several scenarios regarding the future sustainability of supply and demand in Europe. The scenarios were discussed with our advisory board and led to observations on risks associated with the scenarios and investment needs to achieve sustainable supply and demand in Europe.

A.13.1. The global Uranium supply chain for research reactors fuels and targets

The figure below shows the full value chain from uranium extraction to pharmaceutical delivery. Greyed-out elements indicate aspects not under consideration in this study. Note that the process from enrichment to fuel fabrication is also excluded (grey): until now, most of the research reactors used HEU from stockpiles as input for both fuel and target manufacturing, but more and more are converting to LEU³²⁹.

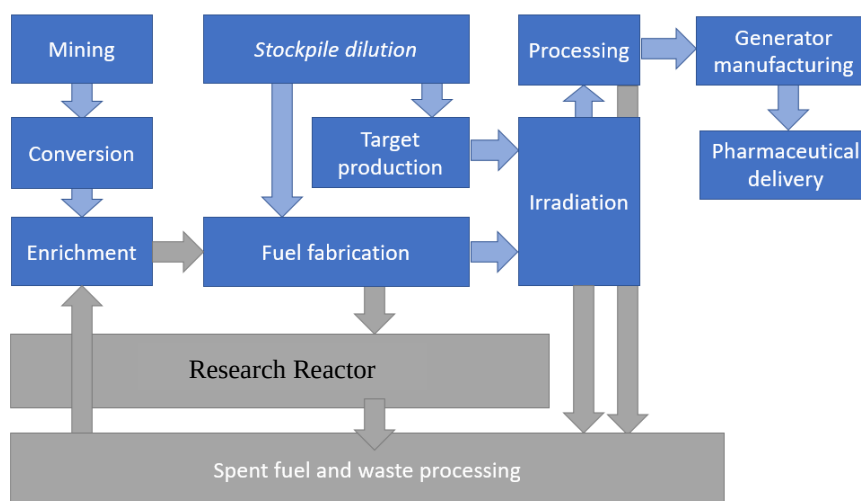


Figure 106: flowchart of the international uranium – Tc-99m supply chain

Uranium mining

The figures below³³⁰ portray the natural uranium availability against the prices (in 2015) at which the material can be extracted. They clearly indicate Canada and Brazil as the largest deposits of cheap natural uranium. At higher prices, a much more diverse palette of suppliers emerges. This leads to the conclusion that there is no shortage of natural uranium for the foreseeable future. Moreover, the same study notes that the current uranium resource base is more than adequate to meet both low and high projections of growth in uranium demand to 2035.

³²⁹Euratom Supply Agency (2016) – Report of the Advisory Committee to the Euratom Supply Agency on Securing the European Supply of 19.75% enriched Uranium Fuel

³³⁰ OECD, NEA and IAEA (2016) - Uranium 2016: Resources, Production and Demand

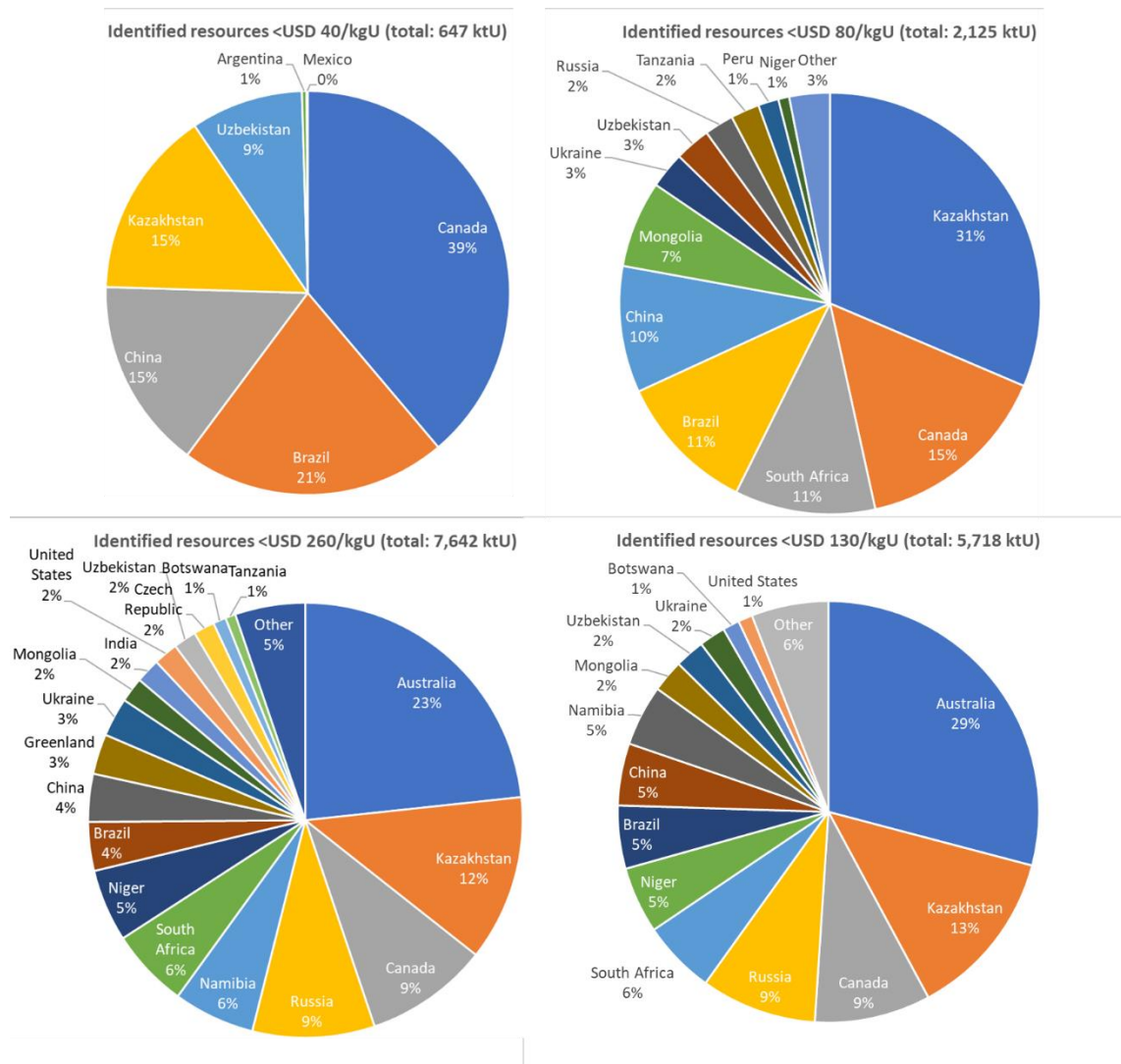
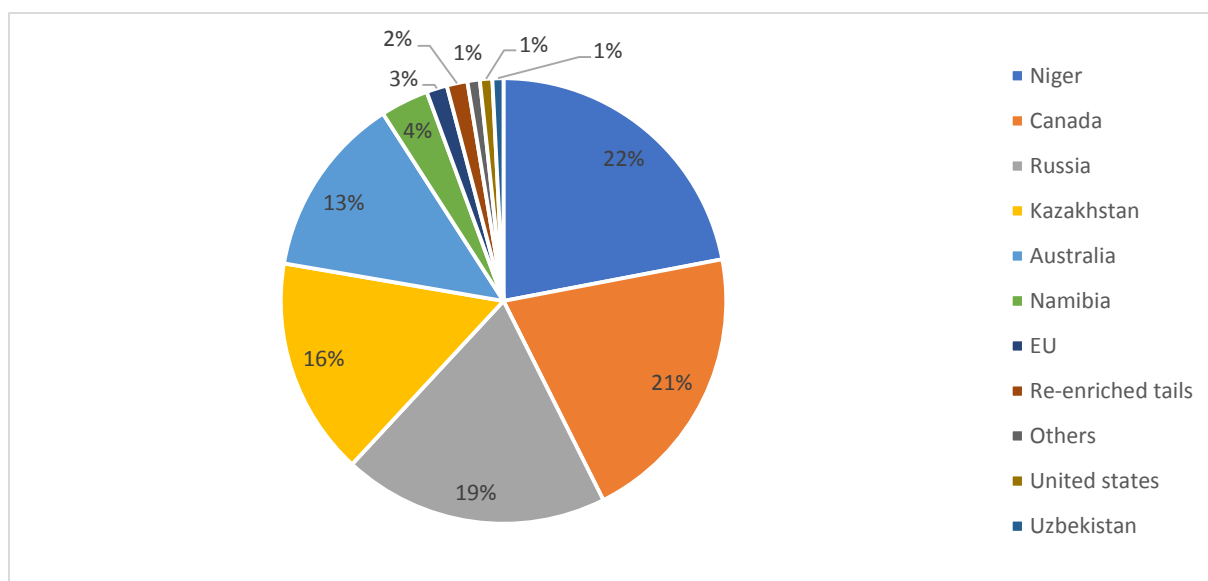


Figure 107: Global uranium deposits per price class (data from OECD-NEA and IAEA, 2016, see footnote)

In 2016 the European Union sourced uranium from a diverse selection of countries, as indicated in the diagram below – there is no dependence on a single country as a supplier³³¹:

³³¹Euratom Supply Agency (2016) Annual report



Also, on the side of commercial suppliers, dependency on a single entity does not exist. The list below shows 17 different commercial entities that supply to the EU.

AREVA NC and Framatome (formerly AREVA NP)	NUKEM GmbH
AREVA Mines	Rio Tinto Marketing Pte Ltd
BHP Billiton (formerly WMC)	Tenex (JSC Techsnabexport)
Cameco Inc. USA	Traxys North America LLC
Cominak	TVEL
DIAMO	UEM
Itochuint	Uranium One
KazAtomProm	Urenco Ltd
Macquarie Bank Limited, London Branch	

Conversion

Uranium conversion services are offered by four major parties that roughly divide the market in two quarters and two fifths (totalling some 93%). Each continent presides over at least one conversion facility.

UF₆ conversion capacity (ESA annual report 2016)

Company	Nameplate capacity in 2015 (tU as UF ₆)	Share of global capacity (%)
Comurhex (AREVA) (France)	15000	25.4
ConverDyn (United States)	15000	25.4
Cameco (Canada)	12500	21.2
Atomenergoprom (Rosatom) (Russia)	12500	21.2
CNNC(China)	4000	6.8
Ipen (Brazil)	100	0.2
Total nameplate capacity	59100	100

Nameplate capacity is the intended full-load sustained output of a facility – the actual utilisation may be lower

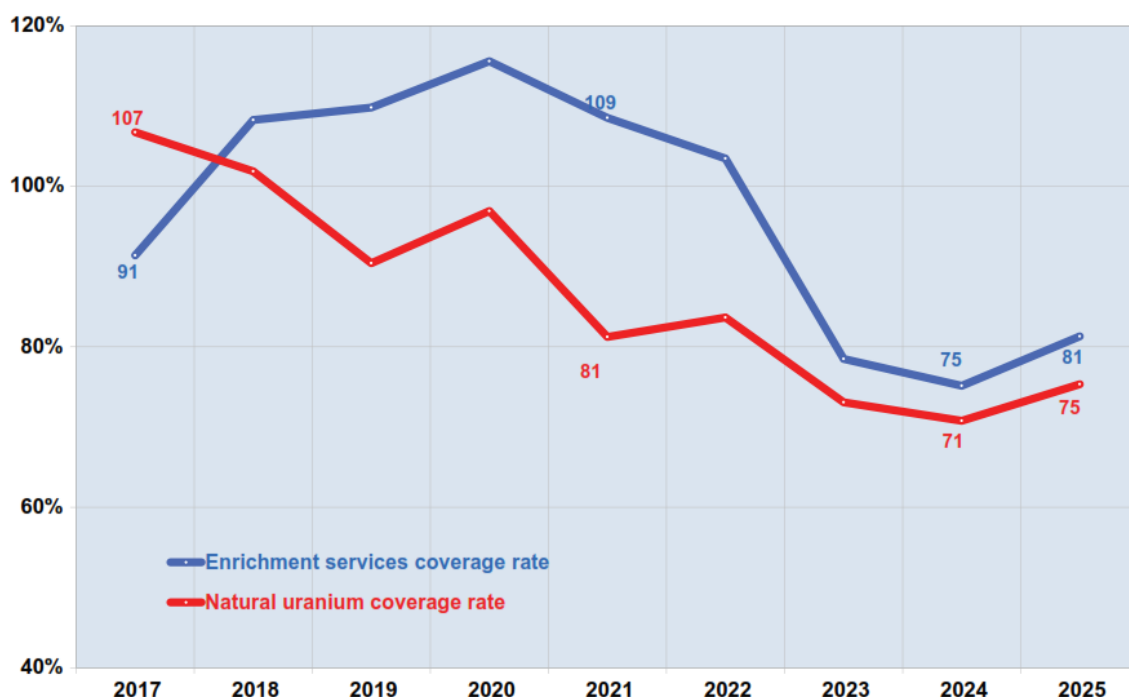
Enrichment

Enrichment services are also available on each continent, as reported by the ESA in 2016. The diversity of suppliers is somewhat limited given the market shares of the largest suppliers that together hold 77% of the market.

Company	Nameplate capacity (tSW)	Share of global capacity (%)
TVEL/Tenex (Russia)	26600	45
Urenco (UK/DE/NL/USA)	19100	32.3
Orano-GBII (France)	7500	12.7
CNNC (China)	5800	9.8
Others* (CNEA, INB, JNFL)	175	0.3
World total	59175	100

Nameplate capacity is the intended full-load sustained output of a facility – the actual utilisation may be lower

With the figures above, the ESA concludes in 2016 that the EU will have security of supply until 2020 for natural uranium (contracts cover over 100% of demand) and enrichment (varying from 91% in 2017 to 116% in 2020), as shows the graph below:



Note must be made that the world's nuclear power generation fleet is expected to double in capacity by 2040³³². This affects research reactors only partially: as we will see below, both their fuels (19.75% enriched LEU or HEU) and targets are produced from a parallel supply chain: diluted (military) stockpiles of HEU that originate (only) from the US and the Russian Federation.

Research reactor fuel and target fabrication

Research reactor fuel production has been a particular object of study by the ESA in 2016. The foreword states that "the worldwide supply of LEU, at 19.75 %, destined for research reactors and the production of irradiation targets is hardly secured in the long term".

Research reactors use fuels that are designed to minimise heat generation and maximise neutron production (or other relevant parameters as desired). As such they employ uranium in metallic form with the highest grade of U235 – 19.75% since the conversion to LEU.

³³² USA DOE Energy Information Administration (2017) – International energy outlook 2017

Dependencies exist

Europe is currently dependent on the United States and Russia for the supply of enriched uranium fuels (HEU and LEU) necessary to run its research reactors and to produce radioisotopes, including in the medical field³³³.

It is technically feasible to produce domestic supply of 1300kg/year in 2025. Adequate knowledge, industrial capacity and suitable sites are available within the EU for LEU enrichment. LEU metal fabrication capacity is not present but technically possible without challenges. However, the experience to do so is “much less available”. Orano (formerly Areva) and URENCO are willing and able to commit to LEU production, but metal production is surrounded by uncertainties.

At a price around €20/g, commercial production of metallic LEU is considered within reach. However, current market costs do not enable investment in metallic LEU production facilities on a commercial basis. This is because the competition from currently available metallic LEU that is produced by diluting military grade HEU. This is much cheaper (at currently €12/g), and it is unclear whether end-users would accept a price increase of 66% to pay for security of supply.

On a legal note, EU production is consistent with international treaties and can be made consistent with EU/national legislation. The establishment of an EU supply facility for metallic uranium can be made possible on already producing sites in France, Germany, the Netherlands or the UK. A two-year preparatory phase is recommended to make the facilities compliant with local legislations. Some uncertainties remain in the anti-trust domain on a European and global (WTO) level as well.

Legal options would be an intergovernmental agreement to build a facility, operated by a consortium that is secured by long-term supply contracts. Buyers would be interested European fuel consumers or a combination of those *and* member states. In both options, failure to secure the funds to acquire the agreed amount of fuel results in payment by the member state that hosts the installation.

Target fabrication

Since their conception, molybdenum production targets have been fabricated following “extremely similar³³⁴” design criteria used for materials testing reactor (MTR) fuel plates (except for adjustments to optimize the transportation to the processing plant and some requirements related to their chemical processing).

CERCA in France fabricates uranium targets for research reactors, also for those reactors producing Mo-99. The HEU targets are supplied by the US supplied and LEU is provided by various suppliers³³⁵. CERCA is a subsidiary of Framatome (formerly AREVA) and the only European supplier of targets. One target supplier in Europe enables self-sufficiency but makes European research reactors dependent on a single company for their operations. Diversification of supply is possible by ordering fabricated targets directly from Russia.

³³³Euratom Supply Agency (2016) Securing the European Supply of 19.75% enriched uranium fuel. Advisory Committee Working Group Report

³³⁴(INVAP, Targets: A Perspective from the Technical and Commercial Point of View, 2013)

³³⁵National Academies of Sciences, Engineering, and Medicine.2016. Molybdenum-99 for Medical Imaging. Washington, DC: The National Academies Press. doi: 10.17226/23563.

A.13.2. Global and European Mo-99 Supply

A.13.2.1. Europe plays a large role in a globalised supply chain

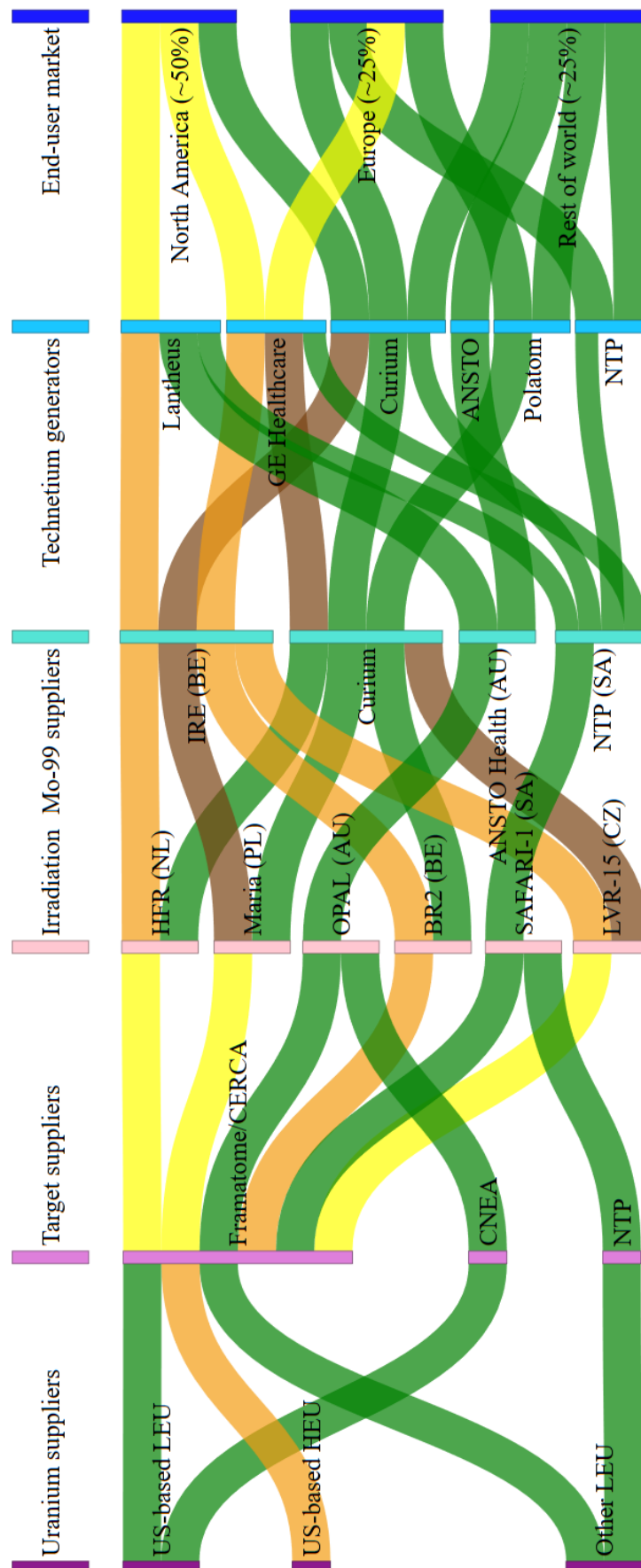
The supply chain for Mo-99/Tc-99m is international as is shown below in the visualisation based on the US National Academies of Sciences (NAS)³³⁶. The irradiation service suppliers, currently dominated by nuclear reactors, supply their Mo-99 through commercial Mo-99 suppliers who deliver their product to Tc-99m generator suppliers. Companies from Australia, Europe, North America and South Africa are involved. Through these steps the product is distributed internationally. Most of the total output ends up in North America (~50%), followed by Europe (~25%) and the rest of the world (~25%). (Market shares are adjusted as compared to NAS, 2016, based on interviews for this research)

The supply chain and the product streams are visualised in for 95% of all Mo-99/Tc-99m production and supply (see next page figure).

The study also showed that European reactors constitute 60-70% of global available production capacity in 2016. This share has increased, as the Canadian NRU that previously had a 19% share, has stopped production. The Mo-99 produced in the European reactors – HFR, Maria, BR2 and LVR-15 – partly ends up as Tc-99m in Europe, while a part is distributed to other continents through Curium (previously Mallinckrodt) and IRE/Lantheus.

³³⁶National Academies of Sciences, Engineering, and Medicine. 2016. Molybdenum-99 for Medical Imaging. Washington, DC: The National Academies Press. doi: 10.17226/23563. The production capacity information in the US NAS report was based on the 2016 OECD-NEA Medical Isotope Supply Review.

Figure 108: The International Mo-99/Tc-99m supply chain (own adaptation of NAS, 2016 – green flows are LEU, orange HEU, yellow both LEU/HEU and brown are backup arrangements)



A.13.2.2. Clear and reliable forecasts are hard to find

The OECD-NEA provides annual updates on the expected supply capacity for Mo-99/Tc-99m, of which their latest is the 2017 OECD-NEA Medical Isotope Supply Review³³⁷. In these reviews, the expected current production capacity of current suppliers is given as well as that of the (potential) future suppliers – an overview of historical expected supply capacity is shown in the following figure. The OECD-NEA is often reported as an authoritative source, although the information given is also criticised³³⁸. Production capacity is reported by suppliers and is often too optimistic. Especially future suppliers have clear incentives to be optimistic about their expected annual production capacity, as well as their expected first year of production. The feasibility of potential future initiatives is not discussed by OECD-NEA, which takes a neutral role. Feasibility is an informed judgement for which one has to rely on experts.

Comparing several successive annual reports of the OECD-NEA, clear shifts in estimates can be observed. The projections for the production capacity in 2010 are much more optimistic than they were in 2016. This is partly due to delay of new initiatives – too optimistic claims at first – and changing expected available production capacity.

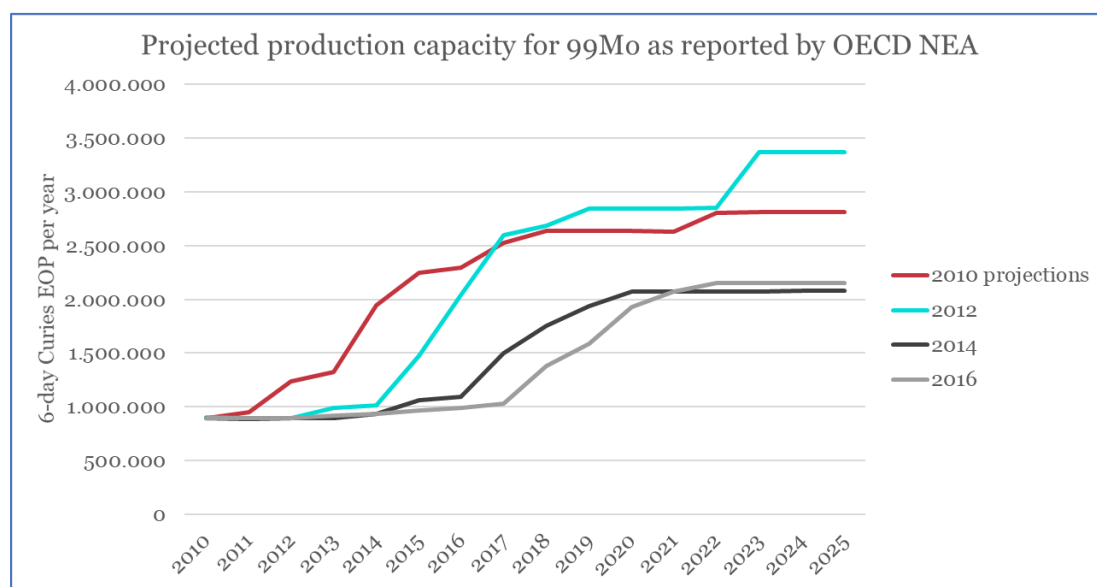


Figure 109: Projections for production capacity for Mo-99 over several years (6-day Ci Mo-99 EOP) as reported by OECD-NEA as published by RIVM (2017) (see footnote)

AIPES, the Association of Imaging Producers and Equipment Suppliers, also make projections of expected production capacity with their own AIPES Mo-99 Capacity Model, previously known as the Versailles model³³⁹. These projections have a weekly resolution and for instance show that the maximum production capacity changes very much every week. The projections for 2017³⁴⁰, predict that in week 42 the maximum global production capacity is just sufficient to meet the weekly global demand of 9.000 6-day Ci

³³⁷OECD-NEA (2017).The Supply of Medical Radioisotopes. 2017 Medical Isotope Supply Review: Mo-99/99mTc Market Demand and Production Capacity Projection 2017-2022.

³³⁸RIVM (2017).Production and use of medical radio isotopes in the Netherlands.Current situation and future outlook. Report in Dutch from the Dutch National Institute for Public Health and the Environment.

³³⁹ National Academies of Sciences, Engineering, and Medicine. (2018). Opportunities and Approaches for Supplying Molybdenum-99 and Associated Medical Isotopes to Global Markets: Proceedings of a Symposium.

³⁴⁰AIPES (2017).World Mo-99 Supply. Presentation given by B. Ponsard, chairman of AIPES Reactors & Isotopes Working Group at the Canadian Association of Nuclear Medicine Annual Scientific Meeting in Toronto.

EOP. On other weeks, the global maximum production is above this global weekly demand. These projections are however made annually and do not predict many years ahead. The data from the AIPES Mo-99 Capacity model are furthermore not that open as the OECD-NEA data, but sometimes graphs from the model are published in literature.

MEDraysintell provides a commercial report³⁴¹ (*which cannot openly be cited*) with some data on current and future production capacity. In their data, local producers are included. Furthermore, some indications of the status of initiatives is given. In the report, somewhat more discussion is given on the feasibility of new initiatives.

Table 43: Current and future suppliers (data from OECD-NEA (2017) except for *, see footnote340)

Reactor	Country	Type	Anticipated Mo-99 production weeks/year	Expected available capacity per year (6-day Ci Mo-99 EOP) by 2022	Estimated end of operation (current)/Expected first full year of production (future)
Current Suppliers					
BR-2	Belgium	Reactor	21	163.800	2036
HFR	Netherlands	Reactor	39	241.800	2024
LVR-15	Czech Republic	Reactor	30	90.000	2028
MARIA	Poland	Reactor	36	95.000	2030
OPAL	Australia	Reactor	43	92.450	2057
RA-3	Argentina	Reactor	46	18.400	2027
SAFARI-1	South-Africa	Reactor	44	130.700	2030
RIAR	Russia	Reactor	50	50.000	>2025
KARPOV	Russia	Reactor	48	16.800	>2025
Future (potential) Suppliers					
OPAL ANM	Australia	Reactor	43	58.050	2057
FRM-II	Germany	Reactor	32	67.200	2054
RA-10	Argentina	Reactor	48	120.000	2021
JHR	France	Reactor	24	115.200	2022
Korea	Korea	Reactor	43	17.200	>2022
Brazil MR	Brazil	Reactor	41	41.400	>2022
CARR	China	Reactor	34	34.000	>2022
MUR/NorthStar Natural Mo	USA	Reactor	52	39.000	2018
MUR/NorthStar Enriched Mo	USA	Reactor	52	>117.000	2018
NorthStar	USA	Accelerator	52	156.000	2020
MURR/GA	USA	Reactor and Selective Gaseous Extraction	52	166.400	2019
SHINE	USA	Accelerator and subcritical aqueous assembly	50	200.000	2020
PALLAS*	Netherlands	Reactor	46	184.000	2025
MYRRHA*	Belgium	Reactor	20	156.000	2036

³⁴¹MEDraysintell (2015). Nuclear Medicine World Market Report & Directory.

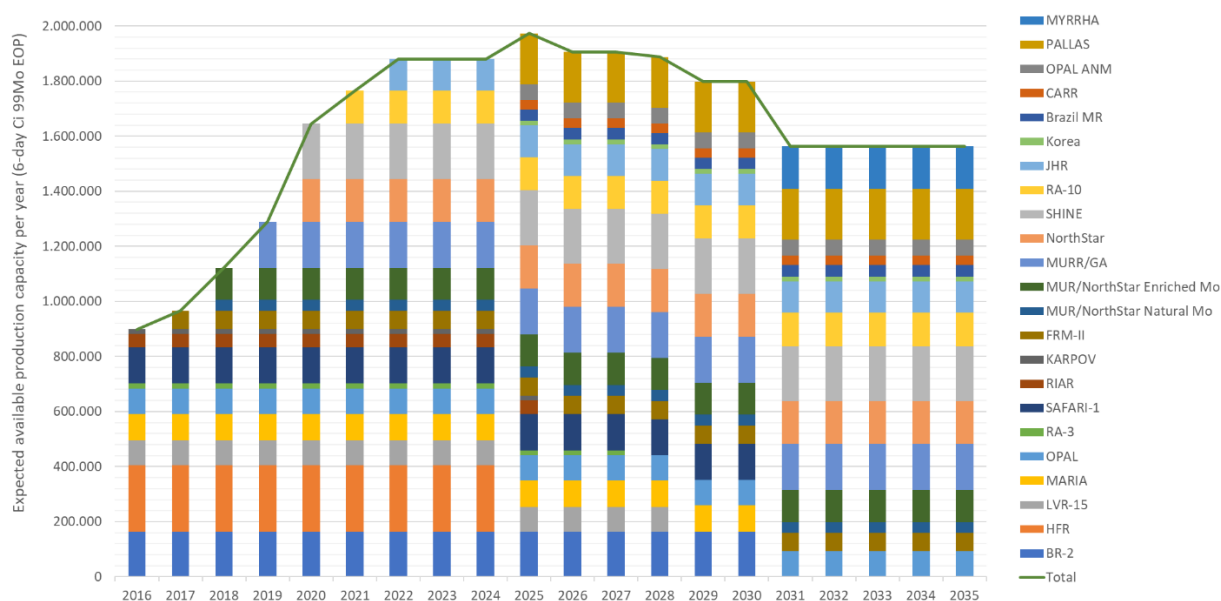


Figure 110: Current and future suppliers (data from OECD-NEA (2017))

A.13.2.3. The drivers on the supply side

The Mo-99 supply chain is complicated as the market is not one at which supply and demand meet each other at a certain clearing price. In fact, some say that “there is no market”. Rather, there is a demand that is mostly always met. In the sector, the success of alternative routes for production of Mo-99 is still a large, uncertain factor. Most experts foresee now that reactor production will be the dominant modality.

The following factors contribute to supply side complexity:

- Opportunistic production by (research) reactors that have idle capacity undermine the market price and investment prospects by adding irregular, low priced capacity. Reactors that currently only produce radioisotopes locally (or none at all) can relatively easily shift their production towards the global market. The Working Group cites for example Russia, South Korea, China, India, Brazil, and Argentina that can take over a part of the global supply chain just as Europe is now supplying a large part of the world. This requires processing capacity to be present at the reactor sites to extract Mo-99 from HEU or LEU targets³⁴²;
- At the same time, capacity cannot be instantaneously added as needed because of mission planning at research reactors. This depends on the “mission mix” of a reactor. In most cases, Mo-99 is a “secondary product”;
- Most research reactors are state-operated installations that usually don’t factor in capital costs for their services. This makes sense for scientific missions but less so for consumable products that have a clear market, such as medical radioisotopes. Waste is another factor that is usually not accounted in the product. However, commercial operators or producers of Mo-99 and Tc-99m would have to finance operations, capital and waste disposal and factor this in the product. This imbalance between state or commercial radioisotope producers distorts the market and “scares off” investors. This in turn makes it hard to foresee whether commercial production of Mo-99 will take place. Most reactors have responded

³⁴²NRG and Curium in the Netherlands have (recently) fully converted their irradiation and processing facilities from HEU to LEU.

that they will in some form introduce Full Cost Recovery (FCR) in the future, but when and to what extent remains to be seen.

- Mo-99 production can create goodwill for nuclear technology as a necessary and peaceful application;
- Demand is a driver for supply to some extent but with extreme time lag (in the case of reactor production) and elasticity. Shortages are shown to be able to dampen consumption by as much as 25% through rationalisation of dosage and application.

Consequences for modelling

As the European Observatory on the Supply of Medical Radioisotopes concluded in 2014, it is extremely hard to model the Mo-99/Tc-99m supply chain or to make predictions about future availability of the material³⁴³. According to information from the European Observatory the OECD-NEA information remains the reference of the market. A modelling approach that closely fits OECD-NEA would both be recognisable and acceptable.

A.13.3. Review of alternatives for reactor-based Mo-99

The development of alternatives for reactor based, uranium target, production of Mo-99 is driven by desires to:

- Reduce nuclear proliferation
- Reduce waste generation, especially high-level solid or high-level liquid waste
- Reduce investment costs in new reactors
- Develop local, flexible production modalities
- Increase security of supply

Methods to reach either or all of these desires can be achieved by using alternative target or irradiation sources. Such combinations consist of 1) using different irradiation sources while continuing the use of (lowly) enriched Uranium targets, 2) using different targets; either natural (24%) or enriched (>90%) Mo-98 or enriched Mo-100, or 3) using a combination of both approaches.

The most feasible target materials are given below:

- (Highly or Lowly) Enriched Uranium
- Mo-100
- Mo-98

Mo-98 is the prevalent isotope with 24% abundance, so Mo-98 targets require little to no enrichment which makes them cheap. 100Mo is a rare isotope with 10% abundance and accordingly the targets are expensive, though they can be relatively easily recycled.

The use of uranium of any kind is associated with proliferation and usually generates solid or liquid waste. The benefit of using Uranium as a target is that the source material is relatively cheap and returns high yields, while the desired Mo-99 is relatively easily chemically subtracted from dissolved fissile material.

Using natural isotopes of Mo omits the proliferation and waste concerns. One alternative is to add one neutron to Mo-98. Such a transformation of natural Mo-98 into Mo-99

³⁴³ European Observatory on the Supply of Medical Radioisotopes (2014) Capacity and Infrastructure development

requires high energy inputs as the *cross section* for capturing a neutron is very small. This requires high neutron fluxes that are typically only reached in reactors. Alternatively, knocking out nuclei from Mo-100 through photon or proton bombardment is possible but this process also requires high power (>100kw), high energy (>40MeV) beams that are difficult to operate in long (days) irradiation times.

Irradiation of these targets takes place in four kinds of irradiation sources:

- Traditional reactors (neutron irradiation)
- Aqueous reactors (neutron irradiation)
- Linear accelerators (Photon irradiation induced by electron bombardment)
- Circular accelerators or cyclotrons (Proton bombardment)

An overview of the combination of potential alternatives is given below:

	Traditional (research) reactor	Aqueous reactor	Linear accelerator	Cyclotron
HEU/LEU	Selective Gaseous Extraction	Medical Isotope Production System (BWX MIPS)	Tritium-Deuterium Fusion-driven (SHINE) Lead-Bismuth spallation driven (NIOWAVE)	-
100Mo	-	-	Photon Induced Transmutation (Northstar)	Proton-induced transmutation (TRIUMF)
98Mo	Neutron Capture (MURR/Norhtstar, GE-Hitachi)	-	-	-

Figure 111: Oversight of potential Mo-99 production alternatives

For each of the combinations of targets and irradiation sources above, we will briefly discuss the drawbacks and benefits.

Alternative approaches have been developed using **traditional reactors**. The **Selective gaseous extraction** method uses Uranium oxide pellets contained in zirconium rods. These rods, after three weeks of irradiation, are then flushed with a mixture of Chlorine and Oxygen gas to produce Molybdenum that can be extracted as gaseous molybdenum oxy-chloride [MoO₂Cl₂]. This process omits the production of liquid nuclear waste and the remaining LEU can be recycled for future irradiations. A drawback is that the process still relies on traditional reactors and the use of LEU. The process is currently being tested by the American FDA for medical applications.

Alternatively, neutron capture by 98Mo targets is feasible when irradiated in high fluxes (i.e. (research) reactors). The target, after irradiation, often has a too low specific activity to be useful in medical applications.

Aqueous reactors use uranium salts dissolved in water as both the fuel and the target. Operated in batches, the reactors are shut down after several days of irradiation after which the Mo-99 is extracted and purified. This process has been developed more recently by Babcock and Wilcox (BWX Technologies) in 2014 as the Medical Isotope

Production System (MIPS), but actual production/commercial operation has not started. An earlier type has been developed and is successfully operated in Russia. The benefits of such reactors are that they are small-scale and easily controlled reactions. A drawback is the production of large quantities of high-level liquid waste.

A sub-critical mode of operation of AHRs is demonstrated by the SHINE concept. Here, a **linear accelerator** drives a deuterium beam into a tritium gas target. The collision results in a fusion that yields neutrons, which in turn cause a chain reaction in the surrounding (natural) uranium target. This in turn yields more (but lower energetic) neutrons that subsequently pass a LEU uranyl sulphate solution. The uranium atoms in this solution, after being bombarded with the neutrons, fission into ⁹⁹Mo and other elements. After days of operation, the solution is stripped from its reaction products and accordingly recycled, which has been reported to be a more efficient use of LEU than in comparison with solid-target based LEU irradiation. The benefit of this approach is the fast and controlled production with relatively low amounts of dissolved LEU used. A drawback remains the generation of liquid waste, though the target solution can easily be reused for future batches.

A similar process is employed in the NIOWAVE Setup, where an electron beam from a **linear accelerator** is used to release highly energetic neutrons from a lead-bismuth target. These neutrons then react with sub-critical LEU to generate Mo-99.

Finally, **cyclotrons** can be used for direct production of Tc-99m through proton-induced transmutation of Mo-100. This production method uses the expensive Mo-100 targets but recovery is very efficient as the produced Tc and can be chemically extracted while the remaining Mo-100 can be recycled.

In table below, we provide an overview of the advantages and disadvantages of the alternative production methods for Mo-99/Tc-99m that we described in this section.

Table 44: Overview of the advantages and disadvantages of alternative production methods³⁴⁴

Alternative production methods	Advantages	Disadvantages
Traditional reactors	+ established or proven technology + fit with current supply chain + high yield + low unit cost + high specific activity	- waste - large capex and investment - negative public perception - historically associated with unreliable outage - government subsidy driven
Selective gaseous extraction	+ less waste + LEU can be easily reused + diversification of supply	- does not fully fit current supply chain - drug regulatory approval and licensing needed - not extensively proven for production
Aqueous reactors	+ small scale reactors + easily controlled process + earlier type successful in Russia + diversification of supply	- large amount of high-level liquid waste - does not fit current supply chain - B&W initiative did not succeed - drug regulatory approval and licensing needed

³⁴⁴ The advantages and disadvantages are based upon those reported in Technopolis Group and Pallas (2016), Delphi Study on ^{99m}Tc Future Supply Initiatives: Reporting to Round 3 Participants.

Alternative production methods	Advantages	Disadvantages
Linear accelerators	+ nearly no waste + lower capex and investment + no proliferation risks + possibly less burdensome regulatory pathways + diversification of supply	- expensive to operate - challenging and unproven technology (for production) - does not fit current supply chain - some have low specific activity - drug regulatory approval and licensing needed
Cyclotrons	+ nearly no waste + lower capex and investment + local production near end-user + uses (modified) existing equipment + diversification of supply	- high cost per dose - inherent impurities - short half-life time product - challenging logistics - drug regulatory approval and licensing needed - many cyclotrons needed for sufficient yield

A.13.4. Global and European Mo-99 Demand

Literature sources can only give us estimates of future demand levels with differing levels of uncertainty. One of the ways to improve the accuracy of the predictions would be to start from an acceptable baseline i.e. a reference or “business as usual” scenario and develop estimates of future demand based on variations in future trends. Both the business as usual assumptions as well as the variations proposed in different scenarios would have to be validated through interaction with experts.

Unfortunately, obtaining comprehensive data to calculate the current demand for the baseline is difficult. Obtaining production/sales data from all manufacturers or purchasing data from all hospitals across Europe is extremely difficult because many suppliers and purchasers are unwilling to share their data. Moreover, Mo-99 and Tc-99m generator supplies are sensitive to distribution efficiency (because of their short half-life) and utilisation efficiency³⁴⁵. For instance, the 2008-2010 shortage resulted in more efficient use of Tc-99m through optimised dosing, more efficient elution of Tc-99m generators, adjustments to patient scheduling, and some increased use of substitute diagnostic tests/radioisotopes resulting in reduction in use and demand even after the supply shortage period was over³⁴⁶. This type of ‘demand destruction’ leads to a highly dynamic balance that constantly adjusts the demand for substitutes according to availability and price.

With respect to using the number of procedures that utilise Tc-99m to calculate demand, it is important to note that changes in the frequency of use of high Tc-99m dose procedures such as myocardial perfusion imaging will have a more substantial effect on Tc-99m usage compared to changes in frequency of use of lower-dose procedures.

In terms of data collection methodology both for estimating current demand and future trends, we can rely on publicly available data and expert opinions based on surveys. In terms of publicly available data, there is a challenge with obtaining reliable and current data for Europe. The Mo-99 market is global and extracting the information of a

³⁴⁵ National Academy of Sciences (2016) Molybdenum-99 for Medical Imaging

³⁴⁶ NEA and OECD (2017) The Supply of Medical Radioisotopes. 2017 Medical Isotope Supply Review: Mo-99/99mTc Market Demand and Production Capacity Projection 2017-2022

particular region in an isolated manner could yield inaccurate results³⁴⁷. Moreover, much of the currently available information is based on expert opinion or referenced from older studies and is hence out-dated. Furthermore, most reported demand estimates are heavily dependent on assumptions regarding the use of Tc-99m in the nuclear medicine market such as the proportion of Tc-99m-related diagnostic procedures among all nuclear medicine procedures or the change in SPECT use. Therefore, a mixed methods approach using publicly available information as well as a survey to bring about a considered consensus of opinion regarding current demand and future trends will be most useful. Nonetheless, it is crucial to explicitly state the assumptions and caveats underpinning the demand calculations.

We present an overview of global and European demand as described in available literature in the next sections. We also provide estimates for the current Tc-99m/Mo-99 demand in EU28 using several estimation routes. Finally, we present demand projections from our survey.

A.13.4.1. Towards an estimate for the current Tc-99m/Mo-99 demand in EU28

We have explored several routes to estimate the current Tc-99m demand in EU28 from available data sources. Due to the very limited availability of good quality data sources, only two routes towards an estimate were feasible. This has resulted in estimates that still include uncertainties. An estimate of the current Tc-99m demand in EU28 serves as a baseline for some of the survey questions that result in relative answers: increases and decreases from the current situation. With such a baseline a quantitative discussion of the future demand is possible, which can feed into the model. Without a baseline, only a qualitative discussion of the future demand is possible. In this section we describe the used methodology to obtain a baseline estimate and the result.

Potential routes to a demand estimate

The current demand for Tc-99m in EU28 can be estimated through several routes. Some routes should *a priori* lead to better estimates due to less assumptions and uncertainties introduced in the route. We have identified the following routes and ordered them from first to third best estimate:

- **An estimate based on the number of generators sold in EU28 and the average generator activities:** information on the sales of Tc-99m generators is not publicly disclosed by generator manufacturers and no information on EU28 level is available. This route would result in the best estimate, the most direct source of information, as there would be very few assumptions needed. However, this route is not feasible.
- **An estimate based on the OECD-NEA's world demand figure and the share of the number of worldwide exams in nuclear medicine in EU28:** this crude approach has been used in literature³⁴⁸ and results in an estimate. The estimate uses the world demand figure of OECD-NEA, which is well-accepted.

³⁴⁷European Observatory on the supply of medical radioisotopes (2014) Working Group 4 (WG4) Capacity and Infrastructure Development

³⁴⁸European Observatory on the Supply of Medical Radioisotopes (2014).Capacity and Infrastructure Development.Working Group 4. July 2014.

- **An estimate based on the injected activity from guidelines and the number of diagnostic procedures with Tc-99m in Europe:** information on injected activity and the number of diagnostic procedures is available but results in information on the total injected activity in Europe. This could be calculated towards a reference figure in 6-day Ci EOP/week³⁴⁹ by compensation for the losses in all transport and production steps until six days after processing. However, that would introduce uncertainties as losses are not well known and differ per country.

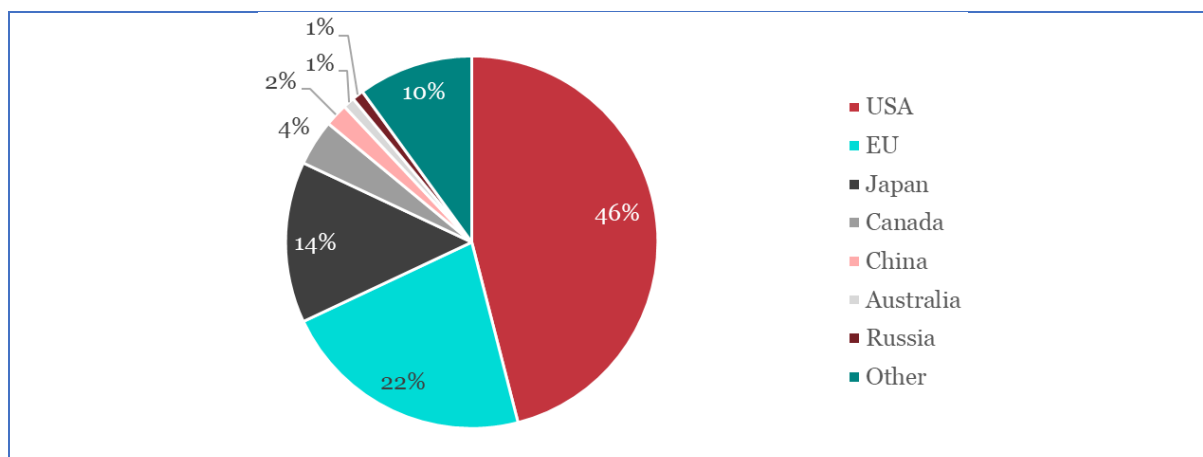
Given the availability of data, we have chosen to further develop route 2 and 3 to estimate the demand. Route 2 will directly give an estimated value of the EU28 demand in 6-days Ci EOP/week. Route 3 will give an estimated value of the EU28 demand in Ci injected – a conversion to 6-days Ci EOP/week is done for comparison.

Route 2: used method and result

According to the latest OECD-NEA Medical Isotope Supply Review³⁵⁰ the world market demand for Mo-99 activity is about 9.000 6-day Ci EOP/week. In the same report OECD-NEA states that there are around 30-40 million examinations worldwide every year that use Tc-99m – which corresponds to 80% of all nuclear medicine procedures.

Based on an often cited 2008 AIPES report³⁵¹ Europe represents about 25% of all world-wide *in vivo* diagnostic procedures using Tc-99m. Khlopkov, Pomper and Chekina (2014)³⁵² used 2013 data from multiple sources to determine the breakdown of world demand for Mo-99 activity by country/region (see figure below). This resulted in an EU demand of 22% of world demand.

Figure 112 Share of world-wide market demand for Mo-99 activity by country/region



Khlopkov, Pomper and Chekina (2014)

³⁴⁹ The reference unit 6-day Ci EOP/week indicates the weekly Mo-99 activity in Curies (Ci) six days after the end of processing (EOP).

³⁵⁰ OECD-NEA HGL-MR (2017). The Supply of Medical Radioisotopes. 2017 Medical Isotope Supply Review: Mo-99/^{99m}Tc Market Demand and Production Capacity Projection 2017-2022. Paris: OECD Nuclear Energy Agency.

³⁵¹ AIPES (2008). Report on Molybdenum-99 Production for Nuclear Medicine – 2010-2020. AIPES. November 2008.

³⁵² A. Khlopkov, M. Pomper and V. Chekina (2014). Ending HEU Use in Medical Isotope Production: Options for US-Russian Cooperation. Nuclear Threat Initiative (NTI). February 2014.

The demand for Mo-99 activity in EU28 is thus between 22%-25% of world demand. This would correspond to **1.980-2.250 6-day Ci EOP/week**.

Route 3: used method and result

In this route the EU28 demand for Mo-99 activity is estimated by using the EAMN and SNMMI guidelines for injected activity, administered activities in EU28 countries and the number of diagnostic procedures with Tc-99m in EU28. This results in a demand estimate expressed in injected activity.

Tc-99m is used in SPECT and SPECT/CT instruments for several diagnostic procedures. Diagnostic procedures differ largely per organ that is being studied – for each type of procedure different activities are injected. Ferrari et al. (2014)³⁵³ give an overview of injected activities for the most common SPECT/CT procedures. They present injected activities as recommended by the EAMN guidelines and by the SNMMI Radiation Dose Tool, supplemented with injected activities reported in some other studies and protocols. The reported guidelines are given as a range between the minimum and maximum injected activities recommended for a specific procedure. Table below shows these minimum and maximum values and the median value in between (midpoint).

Table 45 Injected activities for several procedures as recommended by the EAMN and SNMMI

Procedure/Organ	Minimum (Ci)	Maximum (Ci)	Median (Ci)	Guidelines
Brain	$1.50 \cdot 10^{-2}$	$3.00 \cdot 10^{-2}$	$2.25 \cdot 10^{-2}$	EAMN
Thyroid and Parathyroid	$2.0 \cdot 10^{-3}$	$1.89 \cdot 10^{-2}$	$1.05 \cdot 10^{-2}$	SNMMI/ EAMN
Cardiac	$8.11 \cdot 10^{-3}$	$3.00 \cdot 10^{-2}$	$1.91 \cdot 10^{-2}$	EAMN
Ventriculography	$1.35 \cdot 10^{-2}$	$2.84 \cdot 10^{-2}$	$2.10 \cdot 10^{-2}$	EAMN
Lung perfusion and ventilation	$6.8 \cdot 10^{-4}$	$3.24 \cdot 10^{-3}$	$1.97 \cdot 10^{-3}$	EAMN
Renal	$2.0 \cdot 10^{-3}$	$6.00 \cdot 10^{-3}$	$4.00 \cdot 10^{-3}$	SNMMI
Bone	$8.11 \cdot 10^{-3}$	$2.00 \cdot 10^{-2}$	$1.41 \cdot 10^{-2}$	EAMN

Based on Ferrari et al. (2014)

In 2014 the European Commission published the Radiation Protection N° 180 report³⁵⁴ which contains country data based on studies between 2004 and 2011. This report contains also country data on administered mean activities for a wide range of diagnostic procedures and the frequencies that these procedures are performed. These data can be analysed to result in minimum, maximum and median administered activities per procedure in EU 28 and the distribution of these procedures in EU28. This information is given in the following table.

³⁵³ Ferrari, M., De Marco, P., Origgi, D., & Pedrolì, G. (2014). SPECT/CT radiation dosimetry. Clinical and Translational Imaging, 2(6), 557-569.

³⁵⁴ European Commission (2014). Radiation Protection N° 180. Medical Radiation Exposure of the European Population. Part 1/2. Directorate-General for Energy, Directorate D – Nuclear Safety & Fuel Cycle, Unit D3 – Radiation Protection. Luxembourg: European Commission.

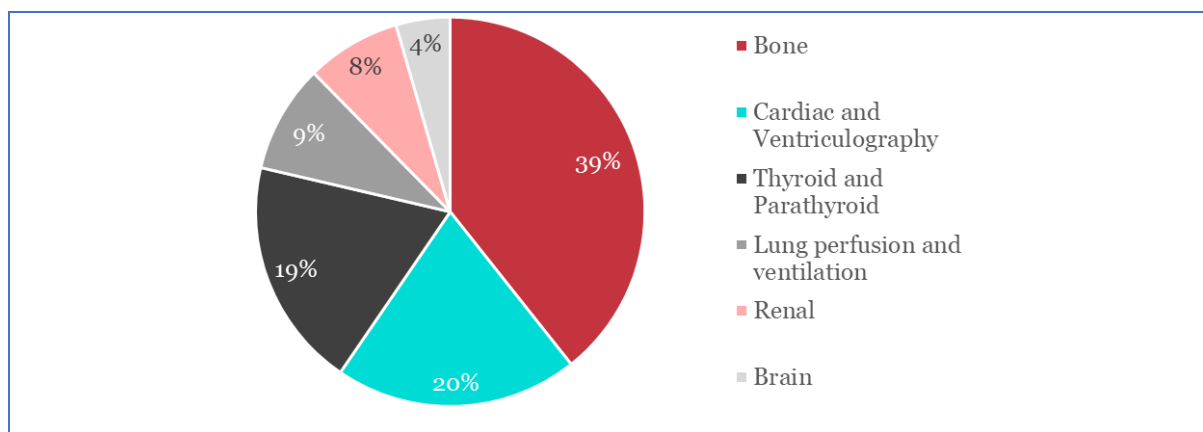
Table 46 Administered mean activities and distribution for diagnostic procedures with Tc-99m in EU 28

Procedure	Minimum (Ci)	Maximum (Ci)	Median (Ci)	Distribution
Bone imaging	$1.40 \cdot 10^{-2}$	$2.08 \cdot 10^{-2}$	$1.79 \cdot 10^{-2}$	38%
Myocardial perfusion	$6.76 \cdot 10^{-3}$	$3.24 \cdot 10^{-2}$	$1.69 \cdot 10^{-2}$	24%
Thyroid and parathyroid imaging	$5 \cdot 10^{-5}$	$4 \cdot 10^{-2}$	$4 \cdot 10^{-2}$	20%
MUGA, cardiac blood pool and flow	$8 \cdot 10^{-5}$	$3 \cdot 10^{-2}$	$2 \cdot 10^{-2}$	2%
Lung perfusion	$2.0 \cdot 10^{-3}$	$7.8 \cdot 10^{-3}$	$4.2 \cdot 10^{-3}$	6%
Renal imaging	$8.1 \cdot 10^{-4}$	$2.5 \cdot 10^{-2}$	$3.86 \cdot 10^{-3}$	8%
Cerebral blood flow	$5.65 \cdot 10^{-3}$	$3.36 \cdot 10^{-2}$	$1.80 \cdot 10^{-2}$	1%
Infection/inflammation imaging	$4.57 \cdot 10^{-3}$	$2.84 \cdot 10^{-2}$	$1.53 \cdot 10^{-2}$	1%

Based on RP180 (2014)

Each procedure has a different minimum and maximum injected activity – and thus a different median injected activity. Therefore, to determine the average injected activity in EU28, it is important to know what procedures are more common than others in Europe. This distribution was reported by Medical Options in their report Nuclear Medicine Europe 2012³⁵⁵ and in the RP180 report. About 54% of all nuclear medicine procedures in Europe correspond to the procedures listed in table 45 – the other nuclear medicine procedures correspond to oncology (44%) and infection (2%). The distribution between the procedures listed in table 45 is given in figure 113 and for the procedures in table 46 in figure 114.

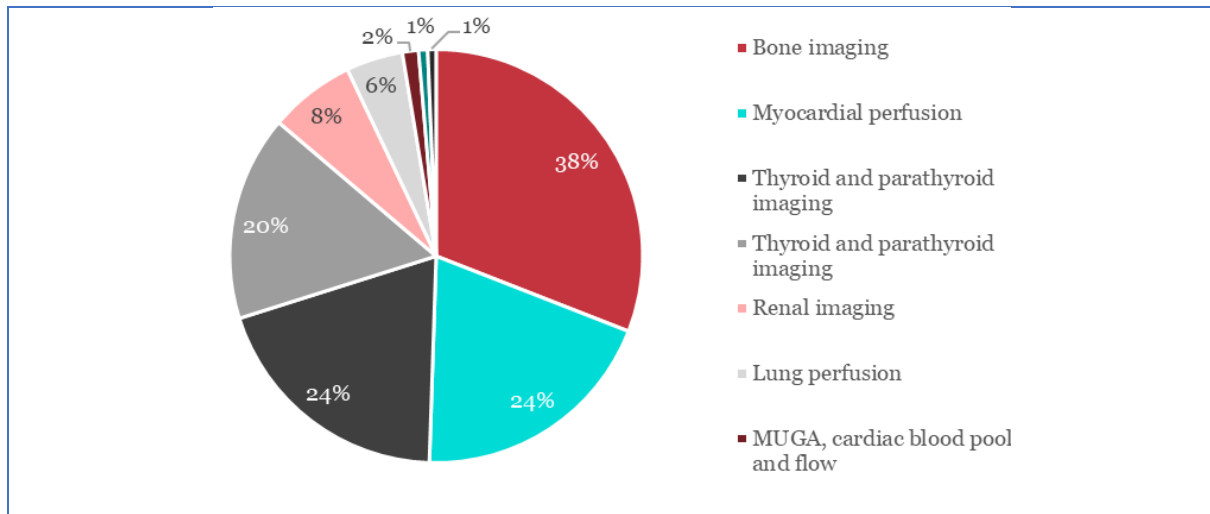
Figure 113 Distribution of procedures in table 45 in Europe



Based on Medical Options (2012)

³⁵⁵Medical Options (2012). Nuclear Medicine Europe 2012. As reported by A. Stephens PhD on <http://www.auntminnieeurope.com/index.aspx?sec=ser&sub=def&pag=dis&ItemID=606759&wf=1501>.

Figure 114 Distribution of procedures in table 46 in EU28



Based on RP180 (2014)

The weighted average injected activity per procedure can now be calculated. The distribution percentage D , given in figure 113, is a function of the procedure p – i.e. $D(p)$. The injected activity A is a function of procedure p as well – i.e. $A(p)$. Now the weighted average injected activity per procedure A_w is:

$$A_w = \sum_p D(p) \cdot A(p)$$

From the median injected/administered activity per procedure we now calculated the weighted average using both the data from Ferrari et al. (2014) in combination with Medical Options (2012) and the RP180 (2014) data. Using the right number of significant figures, this results in:

- For Ferrari et al. (2014) and Medical Options (2012):

$$A_w^{med} = 1.3 \cdot 10^{-2} \text{ Ci}$$

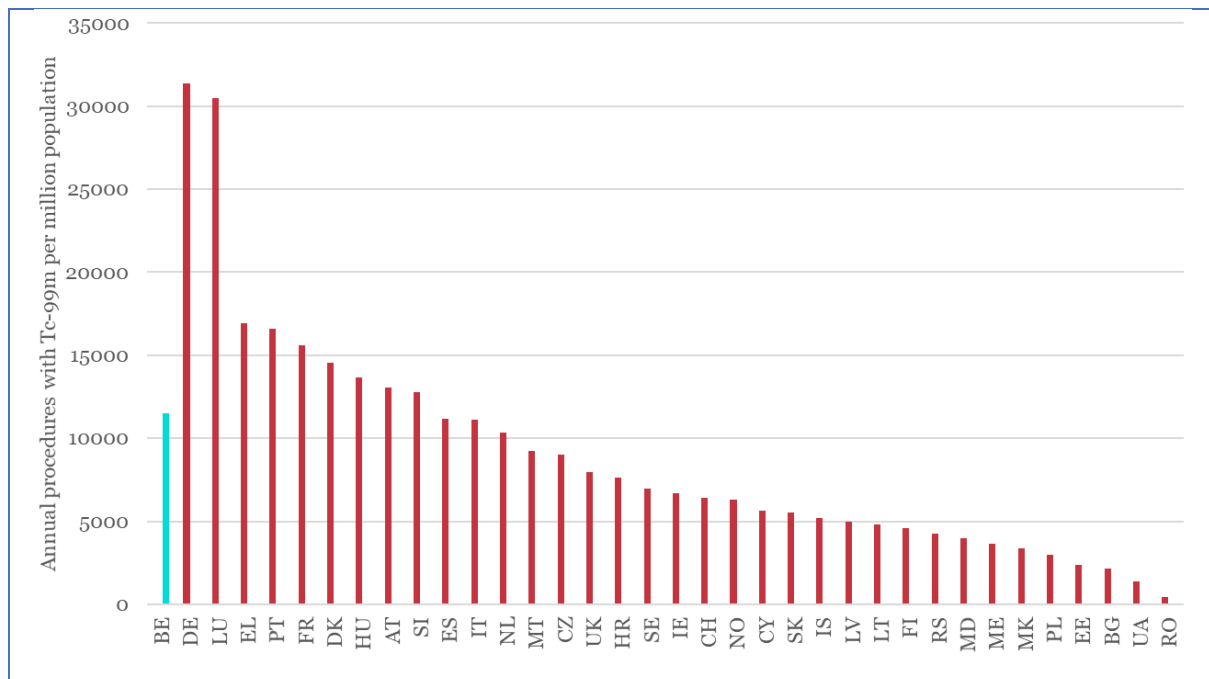
- For RP180 (2014):

$$A_w^{med} = 1 \cdot 10^{-2} \text{ Ci}$$

Both results are very similar, we therefore take as the weighted average injected activity in EU28 $A_w^{med} = 1 \cdot 10^{-2} \text{ Ci}$.

The number of Tc-99m procedures in EU28 can be obtained from the 2014 RP180 report as well. Figure 115 shows the annual number of procedures with Tc-99m per million population for all EU28 countries based on the RP180 data. In this figure, the blue bar for Belgium is estimated from the EU28 average.

Figure 115 Annual procedures with Tc-99m per million population in EU28



Based on RP180 (2014)

An estimate for the current Tc-99m demand in EU28 (D_{in}) can now be calculated by multiplying the weighted averages injected activity per procedure with the estimated number of diagnostic procedures using Tc-99m in EU28 (N_p):

$$D_{in} = N_p \cdot A_w$$

Using the estimated figures, we find the following estimate for **the current Tc-99m demand expressed in injected activity (demand at the patient)**:

$$D_{in}^{med} \approx 7 \cdot 10^4 \frac{Ci}{year} = 1 \cdot 10^3 \frac{Ci}{week}$$

So far, the calculation of the demand estimate in this route has been quite solid and resulted in similar values based on two independent data sources. However, the Tc-99m demand expressed in injected activity is not easily compared to the commonly used reference value of 6-day Ci EOP/week. The calculation of this reference value is introducing uncertainty into the result, as losses throughout the production chain are not well-known, differ per country and depend on many factors. Based on theoretical losses we try to establish an estimate.

This estimate can be converted to a reference value in 6-day Ci EOP/week by accounting for the estimated losses in activity and spillage in each of the stages of the production chain. The theoretical accumulated loss throughout the production chain is given in the following table. In this table the estimated current median Tc-99m/Mo-99 demand for EU28 in every stage is displayed as well (in Ci/week).

The bold figure in table 47 corresponds with the reference value six days after processing: **$1 \cdot 10^3$ 6-day Ci EOP/week**. This reference value corresponds to **11% of OECD-NEA's reference figure for the world-demand for Mo-99 activity**. This is less than expected from the route 2 approach. As said, this figure should be stated with care, as losses throughout the production chain are theoretical and do not necessarily

represent the actual losses in the production chain in EU28 – data on actual losses was not available.

Table 47 Losses throughout the Tc-99m production chain and reference value

Production stage	Cumulative loss	Estimated Tc-99m/Mo-99 demand for EU28 (Ci/week)
Irradiation	0%	$6 \cdot 10^3$
Post-irradiation	-15%	$5 \cdot 10^3$
Transport 1	-22%	$5 \cdot 10^3$
Processing	-32%	$4 \cdot 10^3$
Transport 2	-37%	$4 \cdot 10^3$
Generator manufacturing	-62%	$2 \cdot 10^3$
Transport 3	-66%	$2 \cdot 10^3$
Radiopharmacist	-66%	$2 \cdot 10^3$
Activity injected	-80%	$1 \cdot 10^3$
Six days after processing (6-day EOP)	(-85%)	$1 \cdot 10^3$

Based on standard supply chain durations in OECD/NEA Mo-99 reports and NucAdvisor calculations on generators usage

Discussion of the results of the estimates

The given estimates are the best estimates that could be made with the available data. Route 1, the best approach to get to an estimate of the EU28 demand for Mo-99 activity, was not feasible as no data on generator sales³⁵⁶ could be obtained.

We wish to make the following notes:

- The data used from several sources was collected during a period of 10 years (2004-2014) and do not represent figures of 2017. The estimates are expected to be acceptably close to the current situation.
- The RP180 data contained country information for EU28, but for some countries data was missing. For the total number of procedures using Tc-99m Belgium was missing, this has been accounted for by taking the average number of procedures using Tc-99m per million population and multiplying that by the population size of Belgium.
- The calculations over the stages of the value chain currently assume that the calculated injected activity is the activity prepared for the patient. However, in practice these preparations are often done at the start of the day, while throughout the day the Tc-99m is supplied. The actual injected activity is lower depending on the time of injection during the day. This effect may result in a higher reference figure in 6-day Ci EOP/week but is hard to quantify.
- Following the approach of route 3 with the maximum values of the injected/administered activity per procedure the calculations results in an estimate of $2 \cdot 10^3$ 6-day Ci EOP/week using Ferrari et al. (2014) combined with Medical Options (2012) and $3 \cdot 10^3$ 6-day Ci EOP/week using RP180 (2014). Both are in a similar range as the result of route 2 and correspond to 21% and 29% of

³⁵⁶ The only data found were for generator sales in the United States in 2005, i.e. 92,500 99mTc generators with an average generator size of 10 Ci or 16 Ci, as reported in: NAS (2009). Medical Isotope Production without Highly Enriched Uranium. Washington: National Academies Press.

OECD-NEA's world-demand for Mo-99 activity respectively – which is closer to the share in demand reported in literature³⁵⁷.

A.13.4.2. Current demand from literature and expected growth

There is considerable variation in demand estimates and expected market growth both for Europe and the world. This variation stems from differences in the methodology and underlying assumptions. The tables below showcase global and European demand figures as reported in the literature and the evidence that underpins these calculations. It is important to note that the information sources used to develop demand growth estimates are not strictly independent. Commercially available market analyses are based on information provided by Mo-99 producers, technetium generator manufacturers, pharmaceutical companies, and hospitals. Mo-99 producers and technetium generator manufacturers use these market analyses and other information to develop their own projected demand estimates for business planning purposes. Similarly, reports from independent organisations based their growth estimates on expert groups or surveys of expert opinion. Consequently, there is likely to be some circularity of information and reasoning reflected in various estimates.

Since the number of Tc-99m procedures can be used as a proxy for demand, in the tables below we show global and European data regarding the distribution of nuclear medicine procedures as reported in the literature.

Table 48 Demand and expected market growth for Mo or Tc-99m globally and in Europe as described in the literature

Demand	Evidence Basis	Reference
Worldwide		
Total world Tc-99m dose 11 to 40 PBq (29 PBqavg) considering 1.2 to 4.4% of population/year getting nuclear medicine procedures. For level 1 countries, average 24 PBq	Tc-99m demand was assessed for Germany, Sweden and the US and then used to extrapolate to the world consumption because level I countries' (with 1 physician for <1000) citizens receive 90% of all nuclear medicine examinations worldwide. All data comes from other studies and papers	Kalinowski MB, Tuma MP. Global radioxenon emission inventory based on nuclear power reactor reports. Journal of environmental radioactivity. 2009 Jan 31;100(1):58-70.
The future trend is estimated to fluctuate between two lines, the lowest being a zero growth maintaining the current value, and the highest being a straight line starting at the current value and increasing at a rate of 2.1 % per year until 2020 and 0.5 %/year thereafter.	Based on data from a global survey (713 responses from 52 countries) and an assessment by an expert advisory group, a demand forecast for Mo-99/Tc-99m in 2020 and 2030 was developed.	OECD/NEA (2011) The Supply of Medical Radioisotopes: The path to reliability; also referenced by European Observatory on the supply of medical radioisotopes (2014) Working Group 4 (WG4) Capacity and Infrastructure Development
Average increase of 20% by 2020 from 2010 levels and 25% by 2030 representing an annual growth of 1.8% per year between 2010 and 2020, and of 0.41 % from 2020 to 2030 (assuming linear growth).	Based on data from a global survey (713 responses from 52 countries)	OECD/NEA (2011) The Supply of Medical Radioisotopes: The path to reliability; also referenced by European Observatory on the supply of medical radioisotopes (2014) Working Group 4 (WG4) Capacity and Infrastructure Development
3–8% average annual growth in Tc-	Report of the Expert Review	IAEA Nuclear Energy Series (2013)

³⁵⁷ See for instance: AIPES (2008). Report on Molybdenum-99 Production for Nuclear Medicine – 2010-2020. AIPES. November 2008.

99m demand		
global Mo-99 demand in 2012: 10 000 6-day curies per week ³⁵⁸ 2014: 2012 estimate as starting point, modified annual demand growth rates of 0.5% for mature markets (including EU) and 5% for developing markets 2015 and 2016: 9 000 6-day curies per week from processors 2017: 9 000 6-day curies per week, with 0.5% growth in mature markets and 5% in developing markets Mature markets are estimated to account for 84% of the global demand for Mo-99/Tc-99m, while emerging markets – for 16%.	Panel on Medical Isotope Production, Ottawa (2009). From previous OECD NEA reports; based on information provided by supply chain participants (in 2014), on data collected from supply chain participants (all minus one) on capacity utilisation data during each operating quarter of the period 2012 to 2015 (in 2015 and 2016), confirmation by supply chain participants (in 2017) unknown	Non-HEU Production Technologies for Molybdenum-99 and Technetium-99m NEA and OECD (2017) The Supply of Medical Radioisotopes. 2017 Medical Isotope Supply Review: Mo-99/Tc-99m Market Demand and Production Capacity Projection 2017-2022
The diagnostic radiopharmaceutical market is expected to grow, on average, by 6% a year, mainly driven by volume with limited impact from new tracers.	individual data collection and local estimates	NEA and OECD (2015) The Supply of Medical Radioisotopes. Medical Isotope Supply in the future: Production Capacity and Demand Forecast for ^{Mo-99/Tc-99m} Market, 2015-2020 MEDraysintell (2015) Nuclear Medicine World Market Report & Directory
Europe		
2000 6-day-Ci weekly (Mo-99)	unknown	Koster U. (2011) Present day production of Mo-99 and alternatives. Presentation
In 2008, the world total requirement of Mo-99 was estimated to range between 370 TBq and 450 TBq weekly [10,000 and 12,000 Ci], normalized at <i>t</i> +6d. Europe represents approximately 22% of this total.	Survey based upon individual interviews with current and potential suppliers on their different options: reactor operators, radionuclides processors, radiopharmaceutical products suppliers, and other stakeholders, i.e. AIPES full members and AIPES associated members.	Association of Imaging Producers & Equipment Suppliers Association of Imaging Producers & Equipment Suppliers (AIPES) (2008) Report on Molybdenum-99 production for nuclear medicine – 2010 – 2020
In 2012, 125,000 Ci per year (6-day-Ci), assuming Europe accounted for about 25% of the global demand. Growth expected to be 1.8 % per year between 2012 and 2020, and 0.4 % per year from 2020 to 2030.	Based on estimates from experts	OECD/NEA, 2011; AIPES report (2008) Report on Molybdenum-99 production for nuclear medicine – 2010 – 2020. Referenced in European Observatory on the supply of medical radioisotopes (2014) Working Group 4 (WG4) Capacity and Infrastructure Development

Table 49 Distribution of nuclear medicine (NM) procedures globally and in Europe as described in the literature

Distribution	Evidence Basis	Reference
Worldwide		
Total number of imaging procedures expected to increase by about 35% by 2020 and 50% by 2030 in mature markets	survey	NEA and OECD (2011) The Supply of Medical Radioisotopes. An Assessment of long-term global demand for Technetium-99m

³⁵⁸ A Ci of Mo-99 is not same as a Ci 99mTc. The quantity of 99mTc generated from a curie of Mo-99 depends on the elution pattern. A 9,000 6-dayCi Mo-99 per week market is roughly equal to 41,000 real Ci Mo-99 per week market.

compared to 2010, assuming an average annual growth rate of between 1.1% (2020-30) and 3.0% (2010-20) and that mature markets represent 85% of global market.

- cardiac imaging (12 m/year; mainly Tc-99m, some with Thallium-201);

Expert opinion (probably)

European Commission (DG SANCO) (2009) Preliminary Report on Supply of Radioisotopes for Medical Use and Current Developments in Nuclear Medicine

- bone scintigraphy, including tumour metastases (10 m/year; mainly Tc-99m);

- lung investigation (5 m/year; mainly Tc-99m);

- thyroid imaging and function analysis (5 m/year; Tc-99 or Iodine-123/-131);

- kidney function analysis (Tc-99m);

- tumour staging (PET, 18F-FDG).

Tc-99m is used in approximately 85% of NM diagnostic imaging procedures worldwide.

unknown

IAEA Nuclear Energy Series (2013) Non-HEU Production Technologies for Molybdenum-99 and Technetium-99m

83% NM procedures involved Tc-99m in 2014. 65% in oncology and 33% in cardiology.

individual data collection and local estimates

MEDraysintell (2015) Nuclear Medicine World Market Report & Directory

In 2014, approximately 60% of the world radiopharmaceutical market (in value) was related to Tc-99m-labeled tracers.

Tc-99m diagnostic imaging techniques account for approximately 80% of all NM procedures, representing 30-40m examinations worldwide every year.

unknown

NEA and OECD (2015) The Supply of Medical Radioisotopes. Medical Isotope Supply in the future: Production Capacity and Demand Forecast for ^{Mo-99}/^{Tc-99m} Market, 2015-2020;

NAS (2016) Molybdenum-99 for Medical Imaging. Washington DC: National Academies Press;

NEA and OECD (2017) The Supply of Medical Radioisotopes. 2017 Medical Isotope Supply Review: ^{Mo-99}/^{Tc-99m} Market Demand and Production Capacity Projection 2017-2022

Europe

9m in vivo diagnostic analyses every year in Europe (out of 35m worldwide); So, about 30 000 in-vivo diagnostic procedures involving radioisotopes

European Commission (DG SANCO) (2009) Preliminary Report on Supply of Radioisotopes for Medical Use and Current Developments in Nuclear Medicine; also cited in European Commission Health and Consumers Directorate-General (2009) Preliminary report on supply of radioisotopes for medical use and current developments in nuclear medicine, where it is incorrectly referenced to the

are performed in the European Union per day.

AIPES report (2008).

In 2008, estimated 6-7m (out of 25-30m globally) in vivo diagnostic procedures using Tc-99m annually and annual growth of 1-2% from 2010 to 2020.

Survey based upon individual interviews with current and potential suppliers on their different options: reactor operators, radionuclides processors, radiopharmaceutical products suppliers, and other stakeholders, i.e. AIPES full members and AIPES associated members.

Association of Imaging Producers & Equipment Suppliers Association of Imaging Producers & Equipment Suppliers (AIPES) (2008) Report on Molybdenum-99 production for nuclear medicine – 2010 – 2020

90% of in vivo medical radioisotope use is for diagnosis (imaging) and 10% is for therapy.



Literature research, international conferences, and selected expert interviews

Productiewijzenvoorradionuclidenvoormedischetoepassingen met eenonderzoeks-kernreactorenalternatieve technologieën – TU Delft, February 2009 (Concept) as referenced by European Commission Health and Consumers Directorate-General (2009) Preliminary report on supply of radioisotopes for medical use and current developments in nuclear medicine

In about 10% of in vivo examinations radioisotopes other Tc are favoured because of their specificity for particular use (like Iodine for the thyroid, or Thallium for some heart studies).

Tc-99m is used for over 80% of all NM procedures – 12,000-18,000 Ci/week – demand for Mo-99 is growing by 8-12% per year.

In 2014, 10m (85% of total NM procedures) Tc-99m-based procedures took place in EU28. Of the total 11.8m NM procedures, 3.5m were undertaken in cardiology, 8m in oncology and 0.3m in other areas.

individual data collection and local estimates

MEDraysintell (2015) Nuclear Medicine  World Market Report & Directory

EU27 accounts for 25% (23/1000 people) of global NM procedures.

NM procedures (8.3m in 2013 in total in 35 European countries) split 5-10% therapeutic and 90-95% diagnostic, which in turn are split 15-20% PET and 80-85%

unknown

Charlton, K (2015) Updated 2015-2020 Demystifying the Numbers. HLG-MR Meeting. Presentation

SPECT. 

SPECT is 80-85% Tc-99m-based

Thus, Tc-99m market size between 5.6m and 6.5m procedures with 30K to 0.4K scans per 1m population depending on country

A.13.4.3. Demand drivers

There is a large range of developments that influence demand for Mo-99/Tc-99m. These developments can be described in a qualitative fashion, underpinned with observations and measurements. In the following section, we will describe these developments and indicate what the effect would be on demand of Mo-99/Tc-99m.

Market dynamics: demand as a response to supply/availability

Although theoretically demand could be conceived as an independent variable, it is in fact dependent on the availability of supply: the (perceived) difficulty in acquiring Mo-99 and/or shifts in price will lead to a more rational use of existing supply and/or a search for alternatives, both leading to a lower demand.

The US National Academies of Sciences (2016)³⁵⁹ reports a reduction in demand of as much as 25% after the 2008-2010 shortage based on several OECD-NEA reports and experts. This is due to more **rational and efficient use** (allowing for the coverage of the same number of patients with a smaller quantity of radioisotopes) through:

- increased efficiency in operations: eluting and dispensing doses and reducing decay loss.
- multiple generator elutions per day and scheduling patients throughout the day rather than just in the morning³⁶⁰.
- fewer unnecessary procedures (also driven by changes in reimbursements) e.g the reduction of double rest and stress tests.
- lower dosage per procedure (also driven by stricter radiation safety requirements).

A more critical review of the numbers used could also suggest that the reduction represents a more realistic assessment of the demand. Nevertheless, the effects of these measures are vast. Figure 116 shows the historic development of world demand for Mo-99, with the 25% decrease over the period 2010-2015 following the MR shortage. Such huge variations dwarf demand growth assumptions (commonly 2.1% until 2020 and 0.5% thereafter) in comparison.

³⁵⁹ National Academies of Sciences, Engineering, and Medicine. 2016. Molybdenum-99 for Medical Imaging. Washington, DC: The National Academies Press. doi: 10.17226/23563.

³⁶⁰ NEA and OECD (2011) The Supply of Medical Radioisotopes. An Assessment of long-term global demand for Technetium-99m

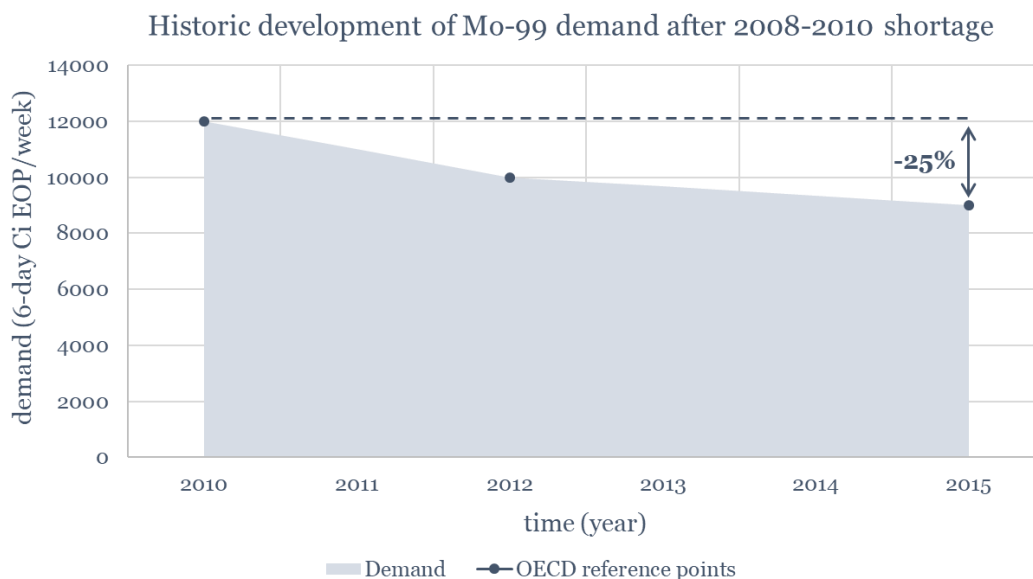


Figure 116: Historic development of the world Mo-99 demand after the 2008-2010 shortage based on NAS (2016) and OECD-NEA reports

Similar behavioural or efficiency changes in the future could lead to a further change in the requirement for Mo-99.

The **search for other modalities**, e.g.:

- PET, because of higher resolution despite of higher costs (in high-income countries). E.g. a PET alternative for bone scintigraphy is available (18F-fluoride), but additional PET scanner capacity would be required which is currently not in place. Also, the available expertise is an issue.
- For myocardial perfusion imaging, Tl-201 can be used, as it was before Tc-99m was widely adopted. Although the technology has lower accuracy and higher required dosage, the quality of Tl-201 images has improved owing to advances in gamma camera design and performance, but there is a lack of training of nuclear medicine experts for this technology. A PET technique using Rb-82 can also be used, but it is expensive to implement and has the same PET capacity issues as bone scintigraphy. Other radioisotopes suitable for perfusion imaging are O-15 and N-13.
- Or non-ionizing technologies such as Ultrasound, or MRI.

An important issue is that with alternative radio-pharmacological procedures, patients often receive higher radiation loads as Tc-99m is one of the least radioactive materials fit for purpose.

Although some Tc-99m procedures may have been temporarily lost to other modalities, such as ultrasound and PET, during the 2008-2010 shortages, it is generally felt that SPECT has regained its market share³⁶¹. This is due largely to the ideal energy and half-life of Tc-99m, lower cost, better cameras and superior images generated. Besides, no practical alternatives exist for a number of techniques including lung ventilation, perfusion imaging, sentinel lymph node localization and paediatric studies. One report

³⁶¹ European Observatory on the supply of medical radioisotopes (2014) Working Group 4 (WG4) Capacity and Infrastructure Development

from Technopolis (2008)³⁶² based on expert opinion on future use of imaging modalities anticipated a decrease in standard SPECT but an increase in SPECT/MRI and SPECT/CT until 2025, keeping Tc-99m demand levels more or less constant. OECD-NEA (2011) supported this outlook stating *"The pace of change away from Tc-99m is expected to be slow and before 2030 there will not be substitution at such a level to actually reduce Tc-99m demand. Other external factors potentially affecting Tc-99m demand will slow historical growth rates but will not remove its overall demand."* There is also potential for developing new theranostic applications, tracers and technology using Tc-99m, but a stable supply of the radioisotope may be a crucial factor in whether such R&D will go forward³⁶³.

One report based on a global survey found that respondents expected substitution of Tc-99m to grow over time (see footnote 361): 11% of the respondents expected that greater than 25% of Tc-99m-based procedures will be substituted by other modalities by 2020 and 27% of the respondents expected a substitution of greater than 25% of procedures by 2030.

Demographic changes

In general, an aging (European) population, is expected to increase the demand for Tc-99m-based diagnostic imaging procedures. Tc-99m tracers are used in oncology, inflammation/infection, and cardiology. In fact, more than 50% of the Tc-99m doses are reportedly used for bone scans while about 37% are used in cardiology.

This should be seen in the context of an expected rise in global per-capita income, rise of middle class, and number of medical practices in Asia and the rest of the world. NEA 2017/NEA 2014 reports an expected growth of 0.5% in mature markets and 5% in emerging markets. With a current division of 84% and 16%, this would lead to 20% global growth until 2030 (with a new division of 75% for mature markets and 25% for emerging markets).

Technological developments

As indicated above, (perceived) supply shortages may lead to substitution by imaging or therapeutic modalities. However, technological developments constantly affect the cost/quality ratio, which influences the willingness to adopt new modalities.

Cost: With the increase in interest for PET, development of Tc-99m-labelled molecules has stagnated with only a few new Tc-99m-labelled molecules under development³⁶⁴. However, more and new tracers would be expected to increase Tc-99m demand because SPECT remains cheaper than PET at the moment.

Quality: Although the development of PET and associated fluorinated agents led to an almost complete halt of SPECT research programmes, the arrival on the market of new high-quality SPECT cameras and the recent SPECT/CT technology is said to increase the demand for SPECT.³⁶⁵

Advances in detectors have been shown to significantly lower doses, and more developments are expected. Especially the single photon detectors (scintillators, solid-

³⁶²Technopolis Group (2008) The medical use of radiopharmaceuticals up to 2025. Report by the Technopolis group (NL), 29 November 2008; commissioned by the Dutch government.

³⁶³ European Commission (DG SANCO) (2009) Preliminary Report on Supply of Radioisotopes for Medical Use and Current Developments in Nuclear Medicine

³⁶⁴Goethals P-E. and Zimmerman R. (2015) Nuclear Medicine World Market Report & Directory. MEDDraysintell

³⁶⁵ According to our experts, supported by e.g. Dave Fornell: Recent Advances in Cardiac Nuclear Imaging Technology, Nuclear Imaging, September 19, 2017

state detectors) can be further improved, and images after detection enhanced with advanced algorithms.

Installed camera base: the installed base of cameras has a replacement period of 5-15 years. The demand for medical radioisotopes is dependent on this base, as switching before end-of-life would be uneconomical.

- The number of installed SPECT cameras is expected to rise from 26,000 (2015) to 29,000 (2025) worldwide
- In high-income/mature markets, such as most of Europe, the installed base of cameras is not increasing – although there are indications that SPECT is being replaced by PET despite its higher costs
- Some of the replaced equipment is shipped to emerging markets, while sales are also increasing for instance in Eastern Europe;
- Also, the use of small specialised cameras, e.g. for breast cancer, would increase demand

Institutional factors

General developments in the medical system will also affect the demand for Mo-99.

- Medical insurance reimbursement policies show a trend towards broader coverage of nuclear procedures, leading to an increase in demand. Especially in the USA, shifting away from the Fee for Service model, where medical facilities get paid per procedure and are thus incentivised to “sell” more procedures rationalises use.
- The limitation of maximum allowed dose to 5mCi in the USA would limit the demand.

A global survey of experts³⁶⁶ revealed that the drivers of increased or decreased Tc-99m in Europe were (in descending order of importance):

Drivers for <u>increased</u> demand	Drivers for <u>decreased</u> demand
the availability of improved technologies	substitute radiopharmaceuticals
stable availability of Tc-99m	increase ease of use/quality of other modalities
increased efficiency	change in cost of Tc-99m imaging
change in cost and increased affordability	availability of hardware and infrastructure replacing Tc-99m-based imaging
	government policies

Table 50 : Demand Drivers

While it could be argued that the factors discussed above would need to be built into a model and ultimately into future scenarios to make them as accurate as possible, we would like to take the position that detail-based accuracy in such a model is illusory. Similar attempts were undertaken by the European Observatory Working Group (2014) and failed. A detailed description of the different factors that influence demand, as described above, is instructive for the general understanding of the problem. Combining these factors, including their interrelationships, in order to come to a quantitative model would yield an intractable, over-complex, and most likely wrong artefact.

Still, even when taking a more modest approach, a major bottleneck in this task is obtaining accurate and reliable information regarding trends and their impact on demand. Literature and/or domain experts (e.g. from industry, diagnostics, radiopharmacy, government bodies, etc.) would be the obvious choices. Much of the information within the literature is out-of-date. Market projections are not readily available.

³⁶⁶ NEA and OECD (2011) The Supply of Medical Radioisotopes. An Assessment of long-term global demand for Technetium-99m

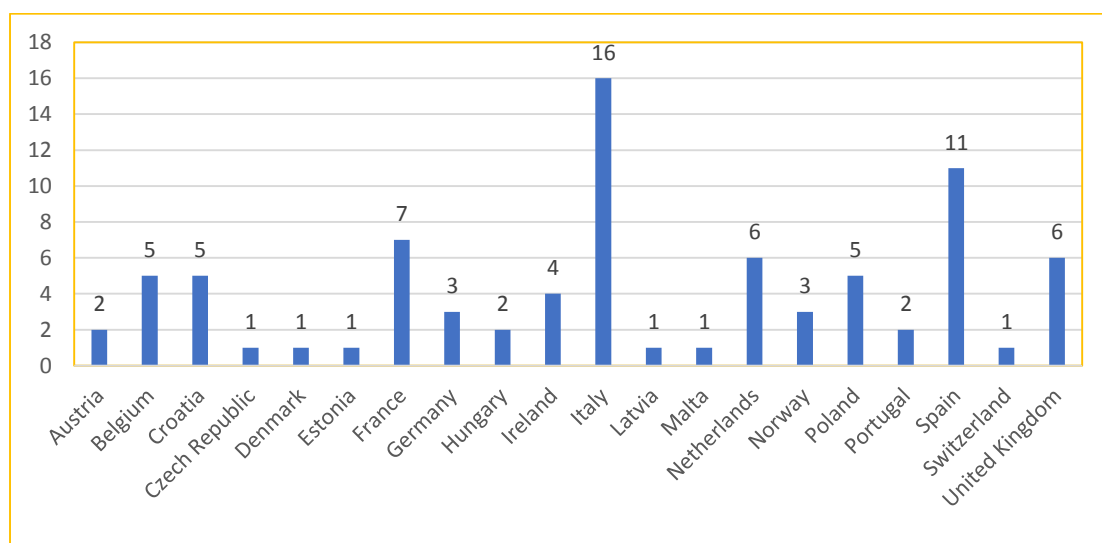
A.13.4.4. Survey on demand expectations

To underpin previous findings on demand, we performed a survey among medical professionals and supply chain experts in the field of medical radioisotopes. The experts were identified in a previous study on the market of medical radioisotopes performed by Technopolis, as well as through national contact points of EANM and ESR. All respondents were asked to identify colleagues with expertise in the field, which yielded a contact database of 500+ experts. These respondents were asked to answer our survey.

In total, we received 83 responses where the Tc-99m demand questions were fully or partially completed. Within this population, almost one-third of the respondents were from Italy (n=16) and Spain (n=11; see figure 117). Among the EEA member states, Bulgaria, Cyprus, Finland, Greece, Iceland, Liechtenstein, Lithuania, Luxembourg, Romania, Slovakia, Slovenia and Sweden were not represented.

The results do not allow for per-country analysis of the demand expectations. A result of 83 answers across EU-28 does not lead to a high confidence level of the findings. However, we believe the findings support existing notions on existing demand, possible alternative uptake, and slow demand growth in the future and as such are worthy of consideration.

Figure 117 Respondents by country (n=83)



Of the 83 respondents, 57 self-identified as imaging specialists working in nuclear medicine. Moreover, 77 of those surveyed claimed expertise in nuclear imaging based on Tc-99m with 64 of the 83 having expertise in nuclear imaging based on other radioisotopes. Please note that respondents were asked to specify all specialisms and imaging expertise that apply to them. Hence, respondents may belong to more than one of the categories specified.

Figure 118 Specialisation of respondents

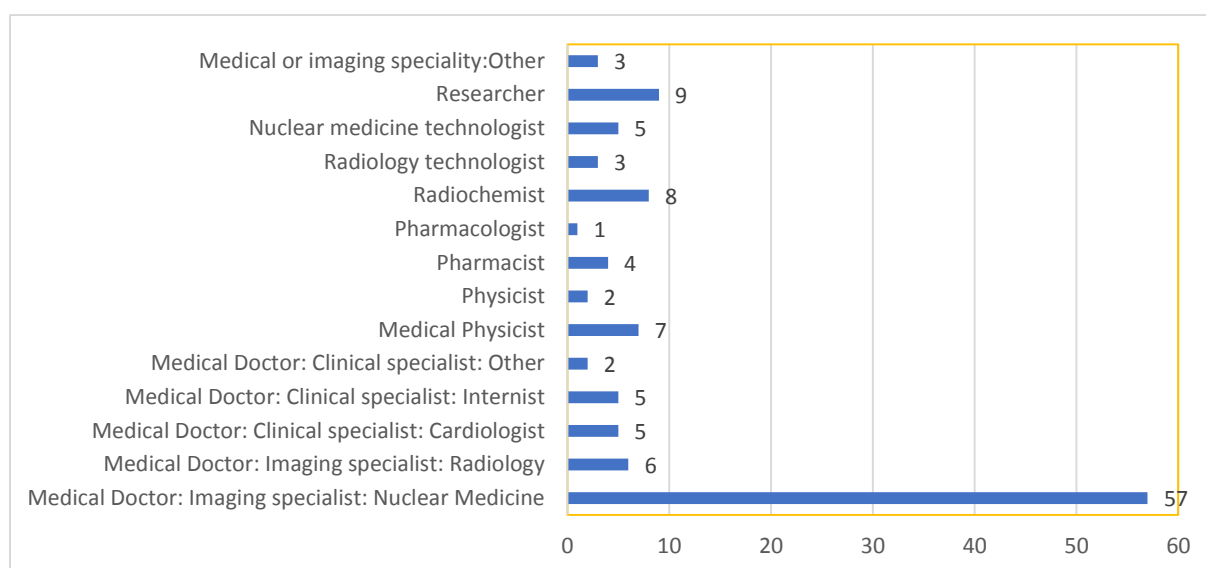
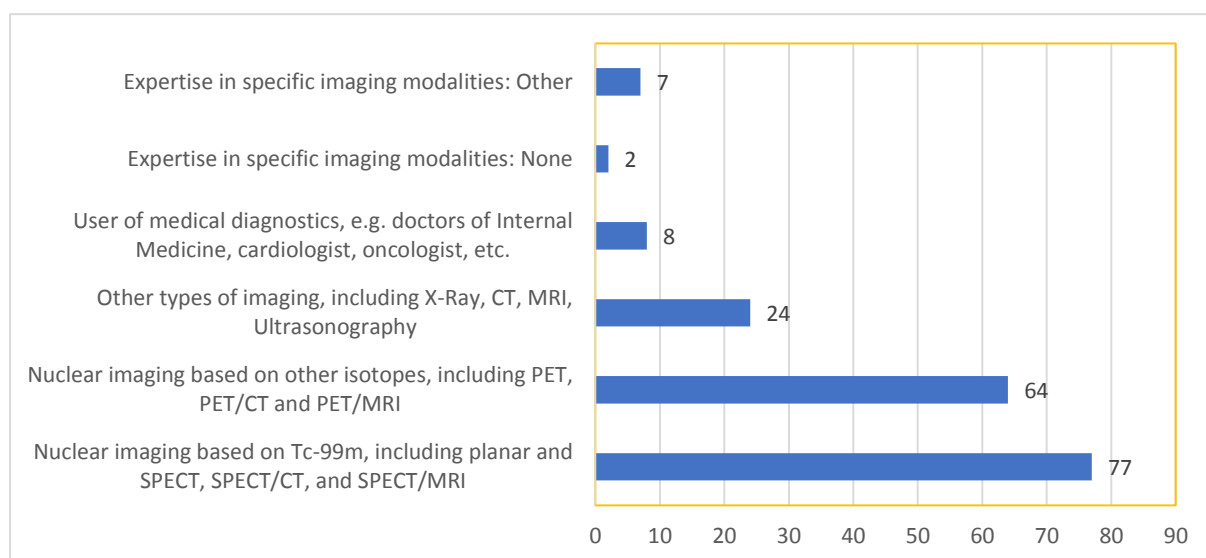


Figure 119 Imaging expertise of respondents

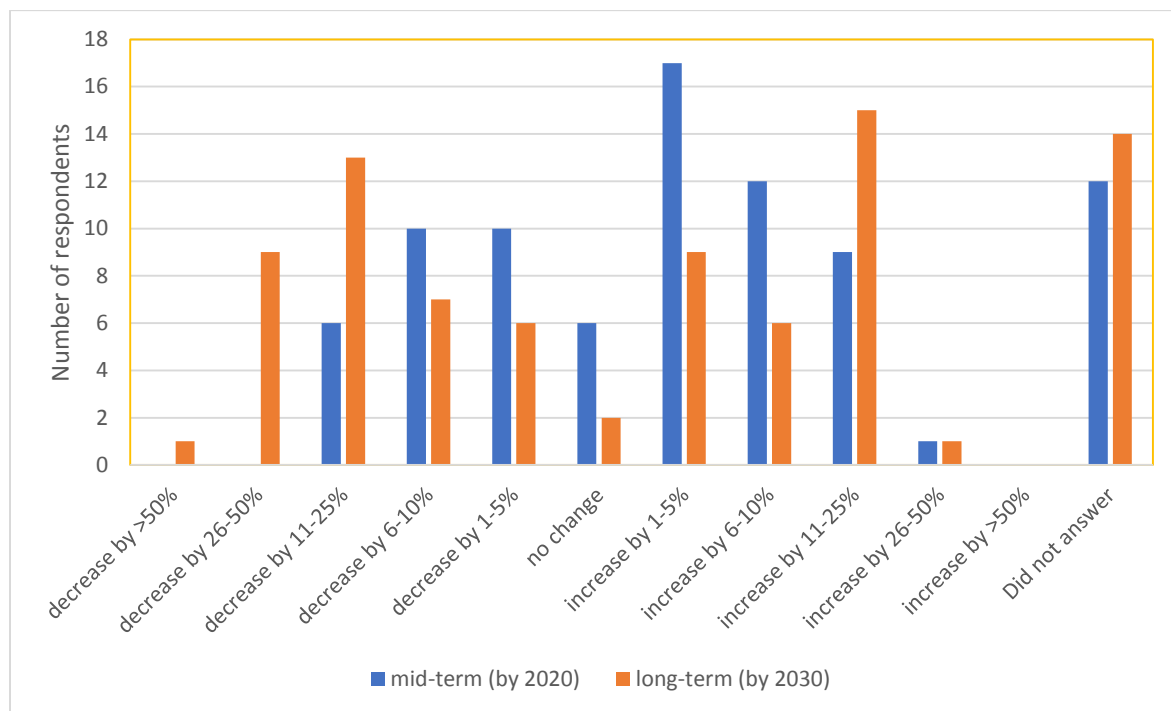


Expected change in use of Tc-99m

A strong consensus on the expected change in the use of Tc-99m in the future was not reached among the survey respondents. In the mid-term, i.e. by 2020, 47% of respondents (n=39) believe that there will be an increase in the total number of diagnostic imaging procedures using Tc-99m compared to 31% who expect a decrease (see figure 120). 20% of respondents (n=17) believe that this increase will be equivalent to 1 to 5%.

In the long-term, the difference of opinion is even smaller. 37% (n=31) of respondents expect an increase in the total number of Tc-99m-based diagnostic procedures, while 43% (n=36) expect a decrease. Furthermore, 18% of respondents (n=15) believe that the number of procedures will increase by 11-25% compared to 16% (n=13) who feel that the number will decrease to the same extent.

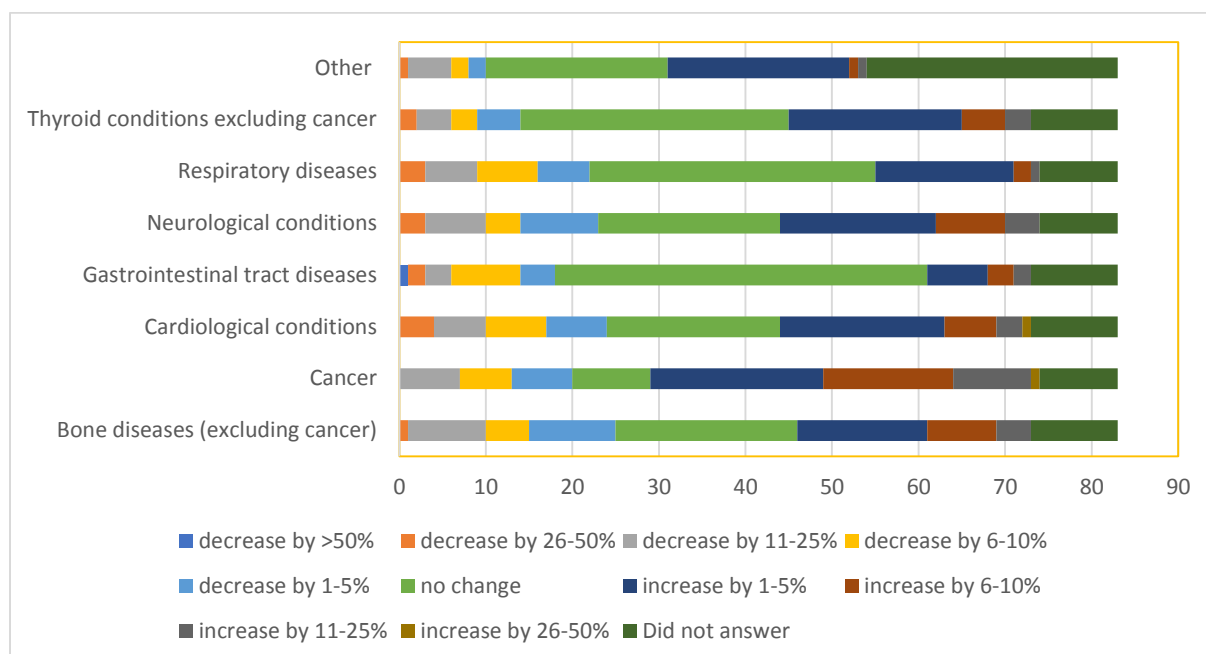
Figure 120 Percentage expected change in the total number of Tc-99m-based diagnostic imaging procedures



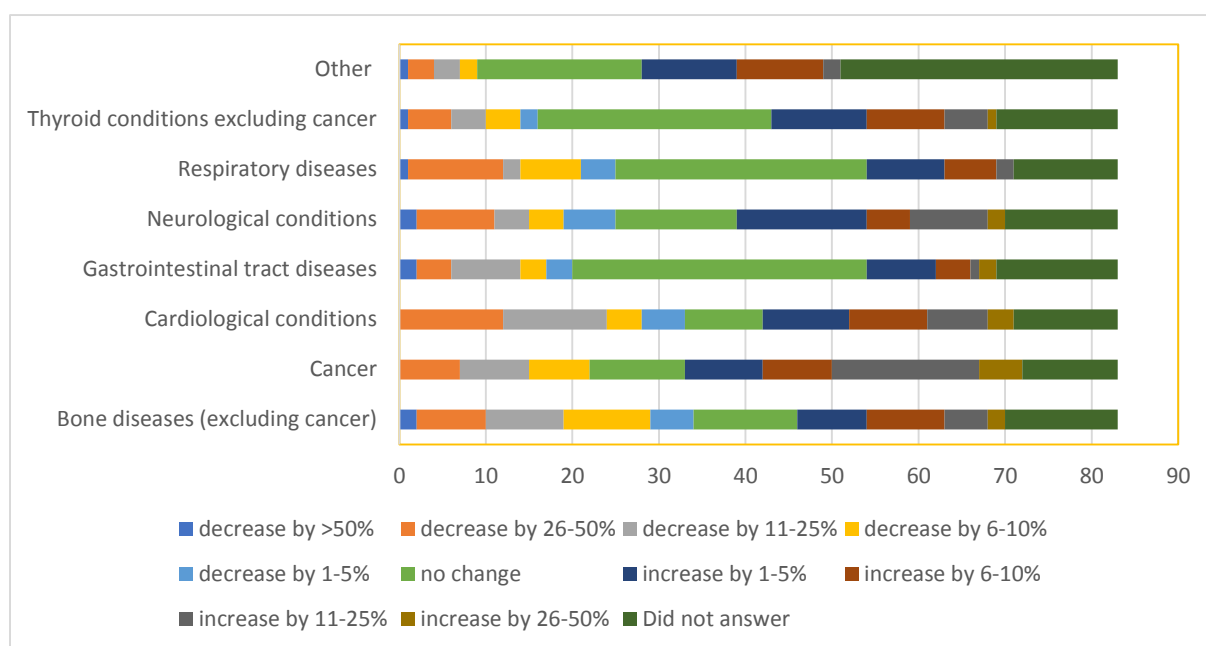
To understand which indications are expected to contribute most to changes in future use of Tc-99m-based procedures, we asked respondents to estimate extent of increase and decrease in number of Tc-99m-based procedures by indications in the medium and long term (see figure 121). Again, it was difficult to find a consensus among the respondents that would convincingly explain a future increase or decrease in the use of Tc-99m for diagnostic imaging.

Figure 121 Percentage expected change in future use of Tc-99m-based procedures by indications (a, medium term; b, long term)

(a)



(b)



For each indication, 12% (n=10, for other indications) to 30% (n=25, for bone diseases excluding cancer) of the respondents expected a decrease in the medium term, while 15% (n=12, for gastrointestinal tract diseases) to 36% (n=30, for neurological conditions) of the respondents expected an increase. For gastrointestinal tract diseases (52%, n=43), respiratory diseases (40%, n=33), thyroid conditions (excluding cancer, 37%, n=31) and other indications (25%, n=21), the majority of respondents expected neither an increase nor a decrease. In fact, the proportion of respondents expecting no change is quite substantial across all indications, which is interesting as this option was less popular when the survey question concerned overall change. For bone diseases excluding cancer, cancer and cardiovascular diseases, there was a very small difference in numbers of respondents (2–5) expecting an increase and those expecting a decrease in future use of Tc-99m-based procedures. For neurological diseases, a slightly greater number of individuals expected a future increase (36%, n=30) rather than a decrease (28%, n=23).

The results for the long term, follow roughly the medium-term trends. However, a clear consensus was observed for bone diseases excluding cancer and cancer where a future decrease (41%, n=34) and increase (47%, n=39) respectively in Tc-99m-based procedures are expected. The majority of respondents expected neither an increase nor a decrease in use of Tc-99m for diagnostic imaging procedures for gastrointestinal tract diseases (41%, n=34). Although this was technically the case for respiratory diseases (35%, n=29) and thyroid conditions (excluding cancer, 37%, n=31) as well, this proportion was not much higher than those expecting a decrease (30%, n=25) and increase (31%, n=26) respectively for these indications. For cardiovascular diseases and neurological conditions, there was a very small difference (n=4 and 6 respectively) in the numbers of respondents expecting an increase and those expecting a decrease.

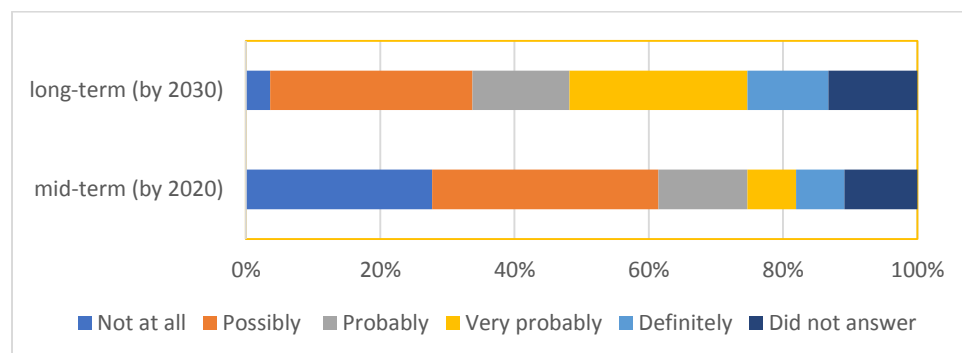
We attempted to investigate the underlying reasons for the respondents' judgements regarding future use of Tc-99m in diagnostic imaging. However, only a maximum of 30% (n ≤ 25) of the respondents ranked the drivers for increased and decreased future demand. Hence, it is not possible to derive conclusions about the reasons behind increased or decreased future demand of Tc-99m.

Substitution of Tc-99m

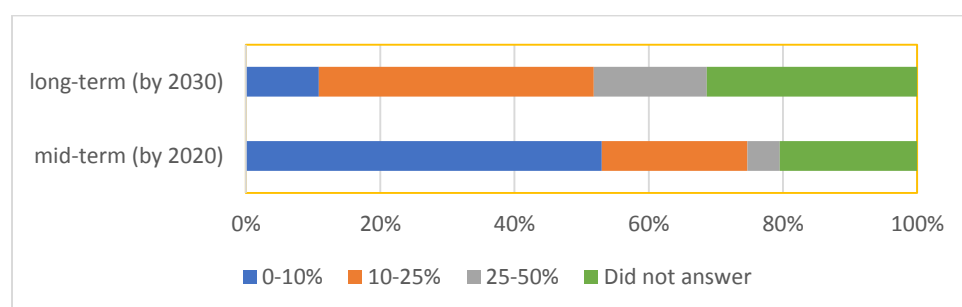
Substitution of Tc-99m through non-Tc-99m-based diagnostic imaging procedures is expected. According to the survey respondents, the likelihood and extent of such substitution is greater in the long term than in the medium term.

Figure 122 Likelihood (a) and extent (in %, b) of substitution of Tc-99m-based procedures

(a)



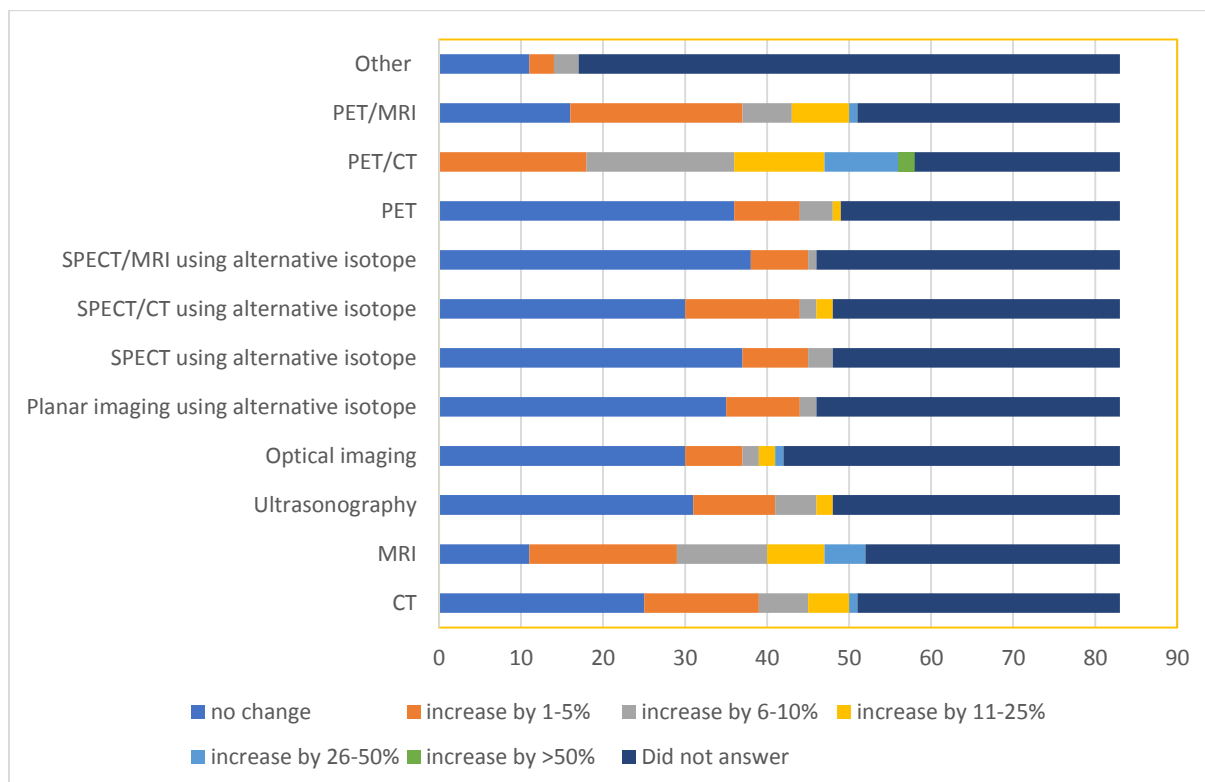
(b)



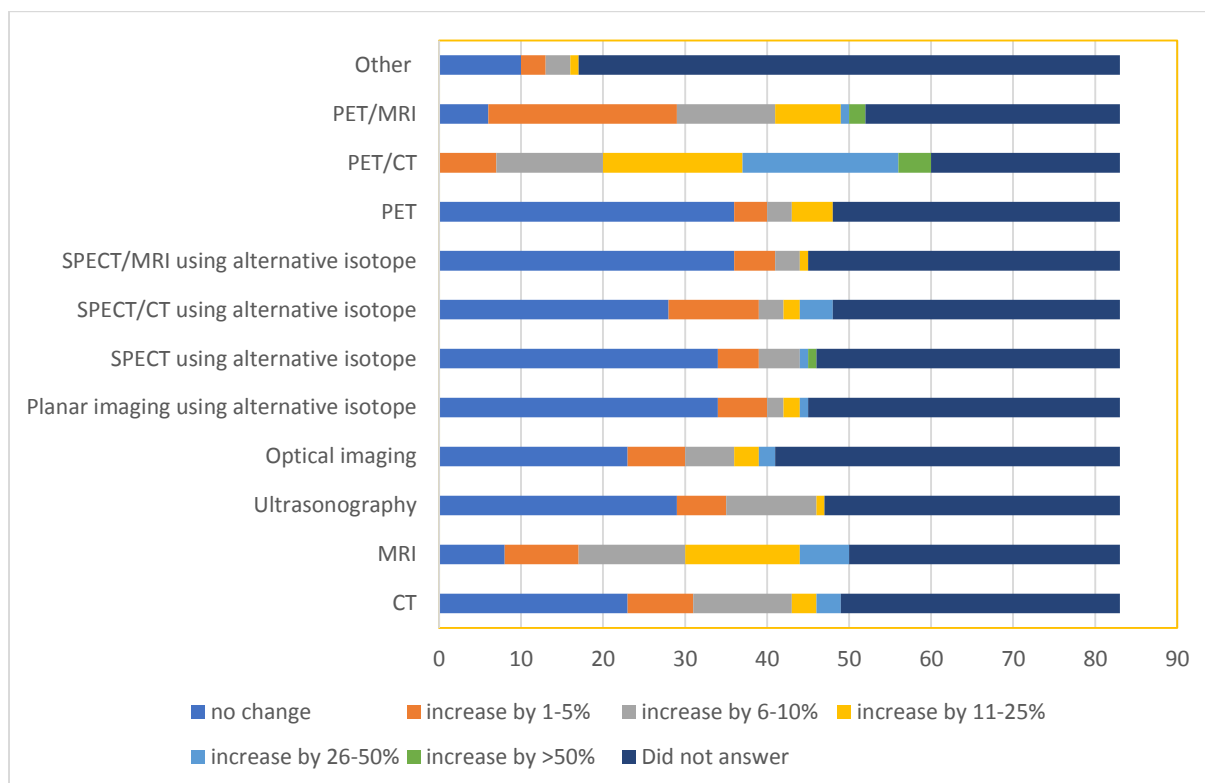
PET/CT, MRI and PET/MRI are expected to be the main substitutes for Tc-99m-based methods in the medium and long term. Moreover, the extent of substitution using these methods is expected to be greater in the long term than in the medium term.

Figure 123 Expected extent (in %) of substitution of Tc-99m-based procedures (a, medium term; b, long term)

(a)



(b)



A.13.5. Modelling demand and supply

A.13.5.1. Multiple sources combined with expert scrutiny improve forecasts

There are several independent sources reporting on future Mo-99 demand and supply. We begin this section with a **review of available sources**. We then describe how we **model a supply curve** on these sources.

The forecast of EU demand and supply for Mo-99 is based on:

- Literature data
- Expert estimates
- Assumptions and taking account of uncertainties

For input data we depart from capacity figures reported by many sources. These figures are compiled into a database that feeds the capacity model, built in Excel to allow easy modification and transfer after project completion.

We have verified with the European Observatory that the figures provided by the OECD-NEA can be considered a trustworthy base for further updating and extending model assumptions. However, a careful choice of variables for the supply-demand model is needed. By only including variables that are likely to have a significant impact on demand and considering expected trends, we are able to keep the model at the right balance between simplicity and realism. Given the large uncertainties in many of the variables, adding more detail would lead to false certainties. Rather, the model should be seen as a first indicator of possible problematic demand/supply situations that merit further inspection. The justification for the model (including caveats) is provided below. The factors affecting supply as well as demand are given in the sections above.

A.13.5.2. Logic of the model

We have modelled the two most critical parts of the supply chain: production of Mo-99 by irradiation in research reactors and processing the irradiated product to bulk Mo-99 solution. The subsequent stage of generator manufacturing is deemed non-critical³⁶⁷ as are six major suppliers as of June 2016, of which three are in Europe³⁶⁸.

The demand and supply model we developed is based on already existing data and models for demand forecasts that are currently employed by other organisations and the input from our demand baseline and our survey. For example, the OECD-NEA already uses a model to forecast the worldwide demand for Mo-99/Tc-99m.³⁶⁹ In their model the main assumption is that the "global Mo-99/Tc-99m demand is assumed to grow at 0.5% per year in mature markets (Europe, Japan, North America, and Republic of Korea)"³⁷⁰.

The supply-demand model starts with the simple equation:

$$Excess = Supply - Demand$$

³⁶⁷ These assumptions have been verified with interviews

³⁶⁸ NAS (2016) Molybdenum-99 for Medical Imaging. Washington DC: National Academies Press

³⁶⁹ See: OECD-NEA HLG MR (2016). The Supply of Medical Radioisotopes. 2016 Medical Isotope Supply Review: Mo-99/Tc-99 Market Demand and Production Capacity Projection 2016-2021. Paris: OECD-NEA.

³⁷⁰ See appendix 2 with model assumptions of: OECD-NEA HLG MR (2014). The Supply of Medical Radioisotopes. Medical Isotope Supply in the Future: Production Capacity and Demand Forecast for the Mo-99/99mTc Market, 2015-2020. Paris: OECD-NEA.

which gives us the parameters E, S, and D to work with. For economic efficiency, we require that E is close to but never actually 0, i.e. we require an equilibrium. The security of supply is factored in later with the Outage Reserve Capacity.

Graphically the model can be represented as the OECD-NEA does. Below we present a graph with the available supply data, mainly based on data from the OECD-NEA. This data is input to the model.

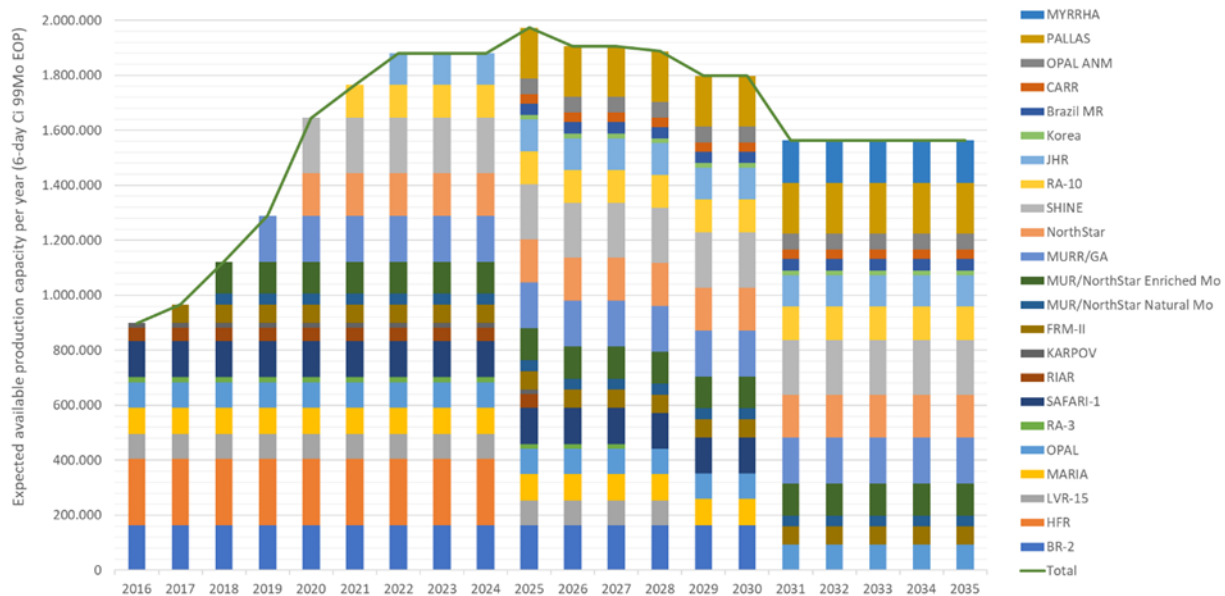


Figure 124: Modelled total annual supply worldwide.

The modelled supply graph is made up of a finite (and relatively small) number of distinct suppliers with intermittent capacity. The sum of all the supplies (maxima) is the green line that varies accordingly.

The modelling task breaks down to mapping out suppliers and their capacity, and the developments that influence demand.

Supply

The supply side is a function of each supplier's capacity and usage over time. i.e.

$$S(t) = \sum_{\text{all suppliers}} \text{Capacity}(t) \times \text{Usage}(t)$$

Capacity per installation can be seen as a constant. **Usage** depends on:

- **Economic considerations** per installation that are challenging to map out. On the one hand, Mo-99 can be produced within a week, at a rather low cost and low complexity. This means that usage can easily be scaled up. On the other hand, we know that Mo-99 production is often state-sponsored. This distorts economic rationales for production. In addition, Mo-99 production competes with more advanced (research) purposes that Mo-99 installations are usually built for. These missions follow a tight schedule that is not lightly interfered with. Therefore, the OECD-NEA advises as good practice to keep outage reserve capacity (ORC) as a buffer at other suppliers when one single supplier fails to deliver.
- **Physical availability:** We also take note of (planned) outages for repairs and upgrades in the usage function. We assume in our model that one single supplier

reserves a fixed amount of capacity per year that is used for 100%. During our research, we shall probe if the suppliers keep ORC. If they do, the usage value is subtracted with the ORC value or:

$$\text{Usage}(t) = \begin{cases} (1-\text{ORC}) \\ 0 \text{ during upgrade/maintenance} \end{cases}$$

- **Outage reserve capacity (ORC):** It must also be noted that supply calculations also need to consider the ORC required to sustain a reliable supply in case of supply shortages. In this study, we follow the OECD-NEA and set the ORC at 35%. This value of ORC differs from the value that is suggested by the European Observatory, which suggests using 100% ORC. We follow the OECD-NEA as their figure for the ORC is based on the analysis of historical data: "Analysis of historical data has shown that the security of supply comes under stress whenever the theoretical maximum available production capacity falls below the level of demand +35% ORC. [...] The NEA believes that the demand curve with +35% ORC is a good representation of a 'safe' level of capacity required to meet market demand with an adequate level of security."³⁷¹
- Furthermore, we foresee the emergence of **alternative technologies** that allow institutions to produce (their own, local) radioisotopes on a much smaller scale – fractions of 0.01% of the European market, for example. For installations employing such technologies, it is not feasible to map them out piecewise.
- One issue for consideration is the role of target processors. We know that European target processing is dominated by two parties that operate multiple sites. How does their (un)availability affect European supply?

Given the short half-life of radioisotopes, an assessment of the chance of shortages on a weekly basis is required. We have thus modelled the global production and processing capacity. Until 2040, a weekly expected production volume is modelled by having installations either produce nominally or not at all (this binary mode is obviously a simplification). Installations can produce less because of breakdowns or other unforeseen shutdown events. These events occur randomly and have a random duration as well. The shutdown duration is normally distributed with selectable parameters for duration and standard deviation.

Demand

As indicated above, the large range of factors influencing demand is not suitable for inclusion in a model. We will assume a similar approach as OECD-NEA and build the demand curve based on assumptions regarding a growth rate that remains constant within a fixed period of time. Thus, the demand function looks as follows:

$$D(t) = \text{Initial demand} \times (1 + r)^t$$

The main input for the growth factor r is the assumption by OECD-NEA of 0.5% annual demand growth in mature markets (Europe, North America) and 3% growth in emerging markets. This assumption was largely corroborated by our Delphi survey. We asked the respondents to assess the OECD-NEA growth assumption, and to provide us with

³⁷¹NEA and OECD (2017) The Supply of Medical Radioisotopes. 2017 Medical Isotope Supply Review: Mo-99/99mTc Market Demand and Production Capacity Projection 2017-2022

estimates for three periods: now-2020 a growth of ~2% per annum, 2020-2030 a growth of 1% per annum, and 2030-beyond a decline of <1% per annum.

For the sake of simplicity, we have used the OECD-NEA growth factors, but have also investigated the sensitivity of this assumption using a higher and lower demand curve for Europe. This means the demand curve would look as follows in three separate scenarios:

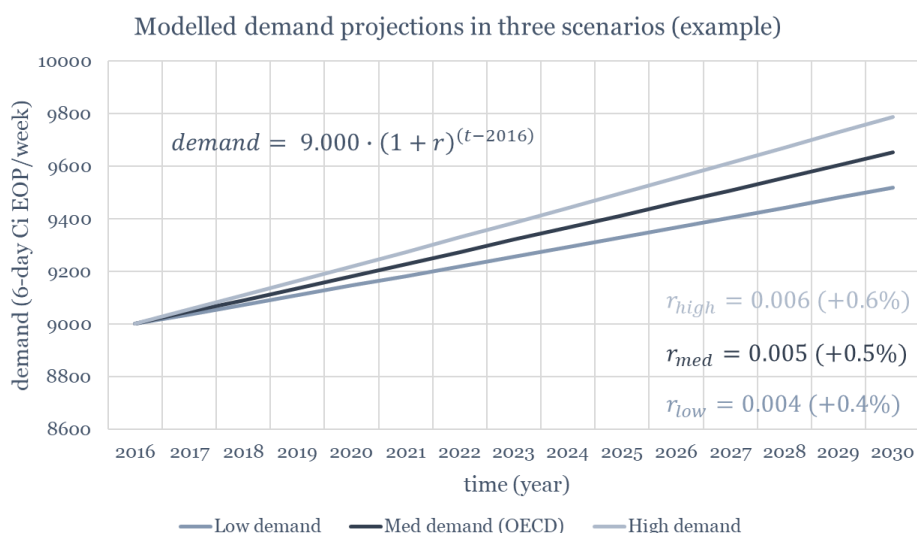


Figure 125: Modelled demand curve.

By comparing demand to supply we can determine whether there is sufficient capacity to foresee Europe in its needs.

A.13.5.3. Monte Carlo simulation

The simulation is based on a Monte Carlo approach. In this Monte Carlo simulation, we run the following experiment:

Given a set of installations (irradiators and processors) that independently operate or break down for a period of 22 years, what is their cumulative production in each week?

We repeat this experiment 1000 times and take statistics over the entire set of 1000 experiments. A single experiment looks as follows:

Table 51 A single experiment in the monte carlo simulation

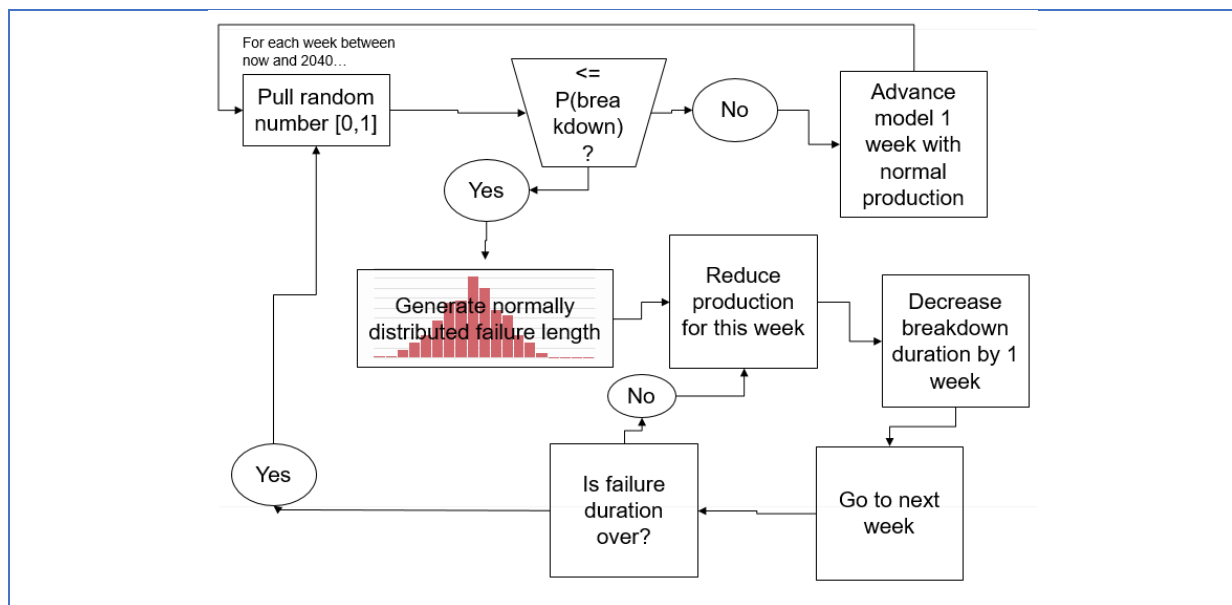
Week	BR-2	LVR-15	FRM-II	...
1	Producing	Producing	Producing	Producing
2	Producing	FAILURE (12 weeks)	Producing	Producing
3	Producing	FAILURE (11 weeks)	Producing	Producing
...	Producing	Producing	Producing	Producing
1143	Producing	Producing	Producing	Producing
1144	Producing	Producing	Producing	Producing

The weekly production capacity is taken from data supplied by the OECD in July 2017. We randomise the chance of failure and the length of this failure by using parameters:

Variable	Parameter	Typical value for reactors	Typical value for processors
Annual chance of failure	A.P(failure)	0.1	0.01
Weekly chance of failure	W.P(failure)	$1-(1-A.P(failure))^{(1/52)}$	$1-(1-A.P(failure))^{(1/52)}$
Mean breakdown duration	MEAN	13	4
Standard deviation from breakdown duration	SD	3	1
Breakdown impact	BDImpact	100%	33%

The primary simulation loop that generates each experiment for one installation is given in the figure below.

Figure 126 primary simulation loop for each installation



The loop begins top-left. Each iteration, for each installation, the software generates a random number between 0 and 1. Each value of the number is equally likely to be chosen. In the next step, the number is compared to the probability of breaking down.

If the number is greater than the probability of breaking down, the installation will perform one-week nominal production. If the number is smaller than or equal to the breakdown probability, we have a breakdown.

In case of a breakdown, the software generates a normally distributed number that stands for the length of the breakdown (in weeks): some breakdowns are longer than others. We round up the generated numbers to positive integer (whole) weeks as breakdown length.

Subsequently, the production for the installation in the week in which the breakdown occurs is reduced with the BDImpact factor – we assume complete shutdown for irradiators, but partial shutdown for processors as they can rely on several independently operated hot cells. In the next step, the breakdown duration is reduced with 1 week and the model advances to the next week. In the subsequent week, the question is asked: is

the breakdown duration over? If not, the production is reduced, and this is repeated until the breakdown is over (small loop in previous figure).

If the breakdown is over, new random numbers are pulled every week until a breakdown occurs (large loop in previous figure).

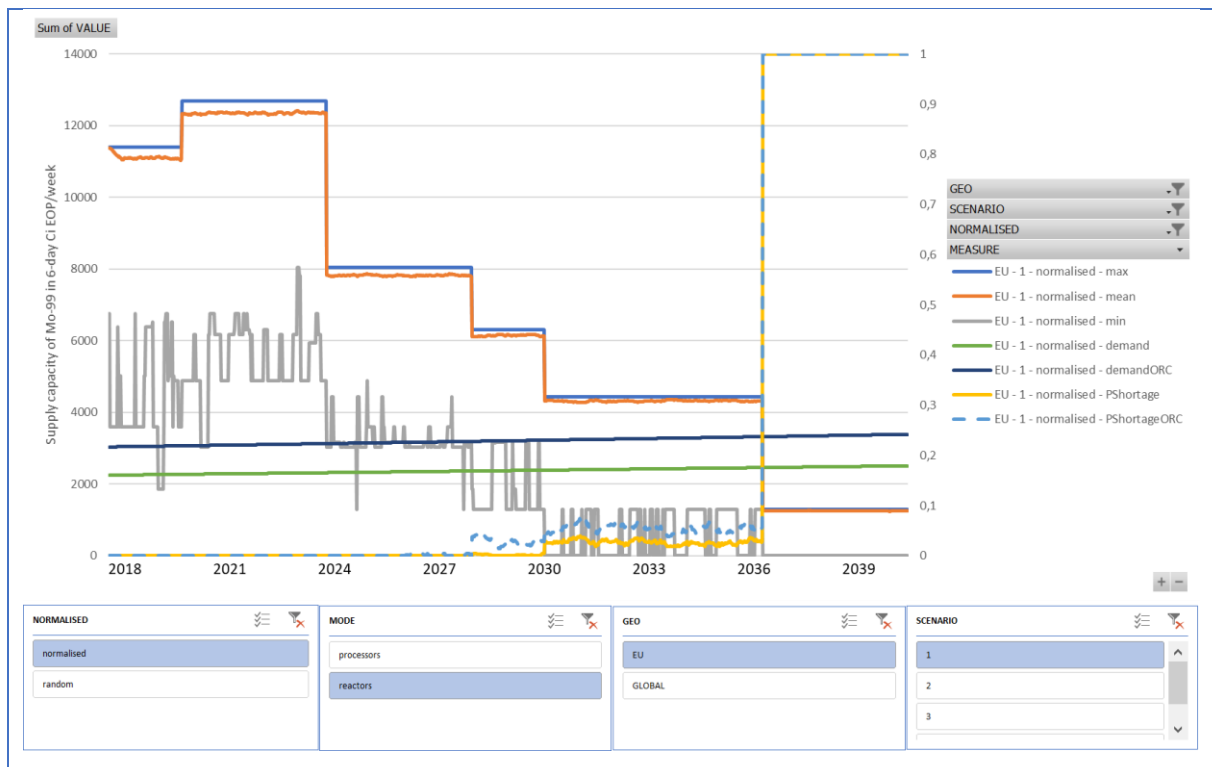
The loop is repeated for each installation in one experiment. One experiment thus consists of 1144 weeks (the number of weeks in 22 years) times the number of installations in the simulation. After each experiment, all the installation's productions are stored in a summary table. This summary limits the computational difficulty for the simulation: a full set of all production values of 10 installations in 1000 experiments would contain 11.44 million values. Such a size is unsuitable for desktop analysis and not necessary either: we demand to know only the sum of global or European production capacity, not the production per individual installation.

A summarised production table looks like this:

Week	Experiment 1	...	Experiment 1000
1	Sum of all installations' weekly production	Sum of all installations' weekly production	Sum of all installations' weekly production
...	Sum of all installations' weekly production	Sum of all installations' weekly production	Sum of all installations' weekly production
1144	Sum of all installations' weekly production	Sum of all installations' weekly production	Sum of all installations' weekly production

We then run summary statistics over all experiments. Usable measures are the mean, minimum and maximum production value. These values are then compared with the actual demand – with and without +35% ORC. When we know the demand, we can count over the 1000 experiments how many times the production was lower than the demand and then calculate the probability of shortages. This is shown in the following figure, which also displays the model implementation layout in Excel.

Figure 127 A preliminary result of the simulated weekly production chart for EU – showing also the model layout



Note that maximum capacity and mean capacity lie close to each other: this indicates the high likelihood of normal operations (low chance of breakdowns). However, if breakdowns do occur, the minimum capacity may be below the demand curve which indicates a possibility of unmet demand.

A.13.5.4. Assumptions

In the simulation we have assumed values for reactor and processor breakdown probabilities and durations with standard deviations. These can be adapted per installation. The values used were confirmed as sensible in our interviews and can be easily adapted.

Furthermore, we know that installations do not run 52 weeks per year (some only 32, for example), but we don't know in which weeks these installations are scheduled to run in the future. To account for this, we have normalised the weekly production. An example: For an installation with a weekly capacity of 100 units, that produces 32 out of 52 weeks we assume that they produce $32/52=61.5$ units for 52 weeks per year.

The breakdown Impact factor (BDImpact) was introduced to account for the possibility that a processor has only 1 of 3 hot cells unusable: the impact factor is then 0.33, the production is then $(1 - \text{BDImpact}) * [\text{nominal capacity}] = 67\%$.

A.13.5.5. Software implementation

As indicated above, the simulation involves a set of several million randomly generated numbers. It is therefore unpractical to generate the production matrix in excel: one would have to copy-paste 1000 summary results of each run into another table, every

time the parameters change. We have selected R³⁷² as it is a common and fast modelling language. However, for further analysis of the output, excel is more user friendly and commonly known. So, we have chosen to use excel to analyse the results of the simulation data generated in R.

The workflow to use the model is:

1. Determine production and breakdown values, modify them in the excel spreadsheet in the tabs "Reactor Parameters" or "Processor Parameters".
2. Run the R-script; once for irradiators and once for processors.
3. Refresh the data connections in excel to have updated values.
4. Analyse data as needed in excel.

A.13.5.6. Caveats

Our assumption of normalised weekly production leads to an overestimation of availability of installations: in the model, all installations are in principle always online. In practice however, the average availability for all reactors is 75% and for EU reactors 60%. This means that of five reactors, usually only three will be online and thus a breakdown of one installation has a higher impact (1/3 of installations) than in the model (1/5 of installations). An implementation of the model can be made without normalisation by assigning random production weeks to the reactors until their quota is filled.

³⁷² R is an open source programming language and can be downloaded [at https://cran.r-project.org/bin/windows/base/](https://cran.r-project.org/bin/windows/base/).

A.13.6. Scenarios for investment needs, risks and impacts

The condition of EU self-sustainability over the medical radioisotope production chain by 2030 is the challenge that these scenarios should address. ***We define EU self-sustainability as the situation in which the scenario's 2030 demand and supply for medical radioisotopes in the EU is at least matched.*** This means that the production and processing capacity of MR in Europe is greater than or equal to the European demand for MR in 2030.

A.13.6.1. Sustainable supply of Molybdenum in Europe – backcasting workshop

To understand the investment needs to secure the supply of Molybdenum and the risks that would need to be tackled under different assumptions of future developments in the supply chain, an advisory board meeting was held in Brussels in the first week of February 2018. We used a scenario-based workshop to address the most salient issues under different future assumptions. The most important questions addressed in this workshop were:

- **To what extent would European self-sustainability be attained under the assumptions of the scenarios?**
- **What investments would be needed to ascertain (an increased degree of) self-sustainability?**
- **What would be the major risks for self-sustainability under such scenarios?**

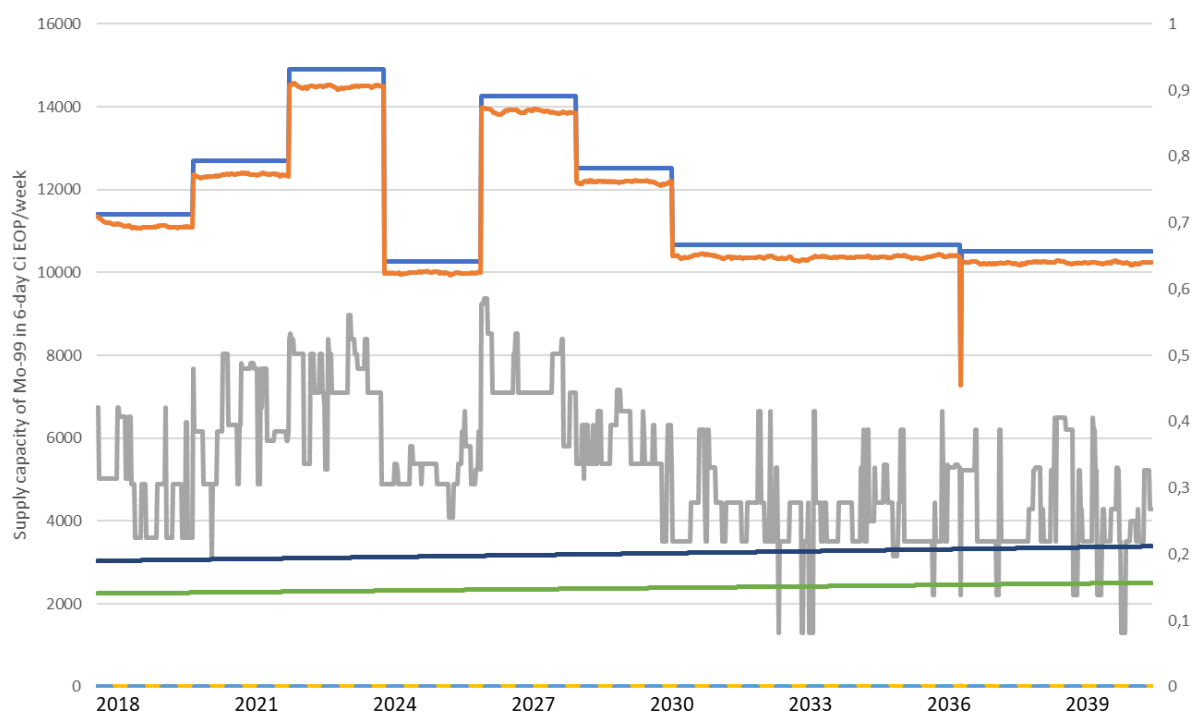
A.13.6.2. Description of scenarios

We developed scenarios that are based on future investment plans for the supply chain, focusing on irradiators and processors. Given a relatively stable demand in the foreseeable future, commissioning and decommissioning plans for facilities determine to a large extent whether local European demand can be met within the EU, thus achieving sustainability. Our scenarios are based on published plans for facilities and an assessment of their likelihood of occurrence based on expert interviews and our own assessments. This leads to scenarios that each lead to a different focus in terms of self-sustainability.

The scenarios **should not be seen as “predictions”**, but as thought exercises that trigger different discussion: what would happen if...? We discussed the scenarios from the least problematic to the most problematic in terms of self-sustainability, to get a sense of the challenges that lie ahead.

A.13.6.3. Optimistic scenario

This scenario entails the completion of all (known) planned irradiation facilities in Europe and the world, including the building of PALLAS as well as MYRRHA. Such a scenario would entail a very low, almost non-existent, probability of short-term shortages until 2030 and a slightly higher probability of shortages from 2030 onward in Europe. No real issues are to be expected. Globally the picture is rather similar: no significant probability of shortages is foreseen until 2040.



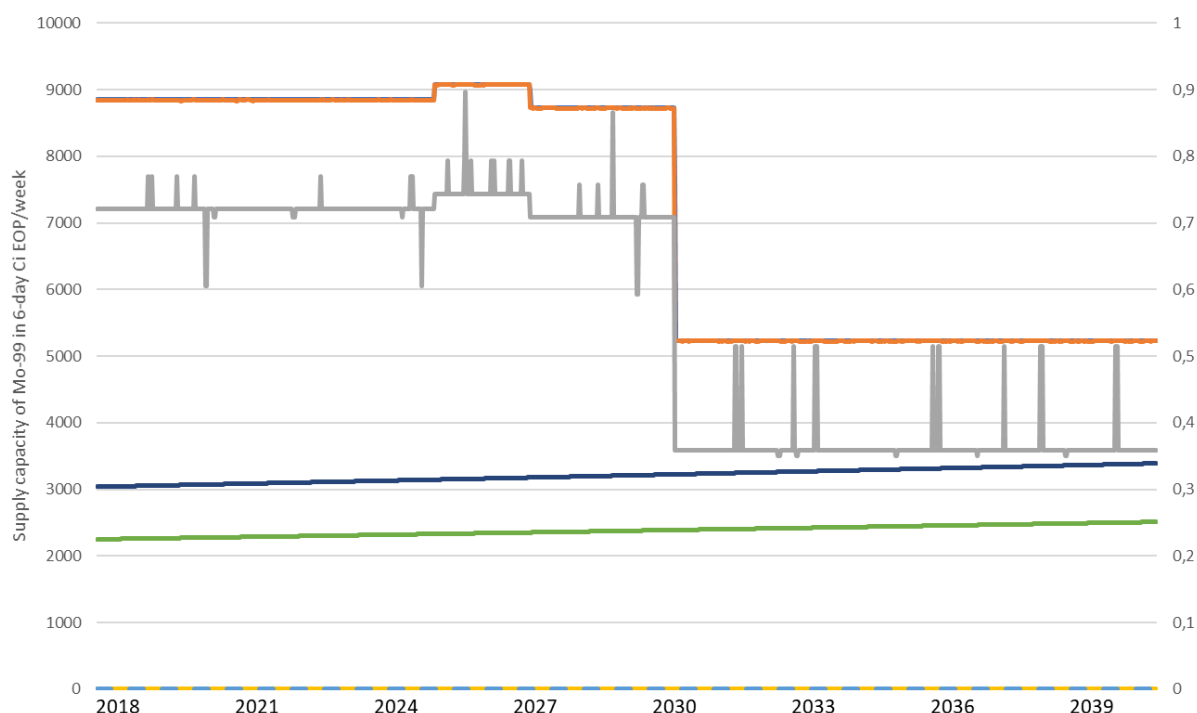
blue, orange and grey lines show production capacity maximum, mean, and minimum respectively– the light blue line indicates the probability of shortage (right axis)– the green line is demand, the dark blue line is demand + ORC). The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability.

Figure 128 Optimistic **irradiator** scenario for **European** supply and demand

This scenario entails large investments in both MYRRHA and PALLAS, which was not deemed impossible by the experts. However, it requires extension of the BR2 reactor until 2036 and a fully operational MYRRHA at that time to take over production from BR2. Furthermore, it was pointed out that the MYRRHA reactor is primarily a research reactor and that availability for Mo⁻⁹⁹ production would be considered a secondary goal for MYRRHA operation, making MYRRHA less reliable than PALLAS – which is primarily focussed on MR irradiation.

In terms of processing facilities, the model shows that capacity is in principle sufficient to prevent any shortages in Europe. In this scenario, the opening of the MARIA processing facility is estimated for 2025³⁷³. Globally the total processing capacity is significantly larger than the demand (+35% ORC), so that there is no probability of shortages foreseen in the model. Although the processing capacity is sufficient, it should be noted that due to geographical constraints and types of targets and processes used by processors, processing capacity at the one place is not necessarily exchangeable with processing capacity at the other place. Currently, the irradiated targets from the polish MARIA reactor are processed at Curium in the Netherlands – that is almost the maximum distance that is possible between a processor and irradiator and also the reason why processors are often close to an irradiator. IRE and Curium use different targets and processes, so that the one target cannot be (easily) processed at the other processor.

³⁷³ The MARIA processing facility completion has shown progressive delays over the years, with current estimates beyond 2023. According to our interviewees financing is not yet certain.



(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively– the light blue line indicates the probability of shortage (right axis)– the green line is demand, the dark blue line is demand + ORC). The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability.

Figure 129 Optimistic **processor** scenario for **European** supply and demand

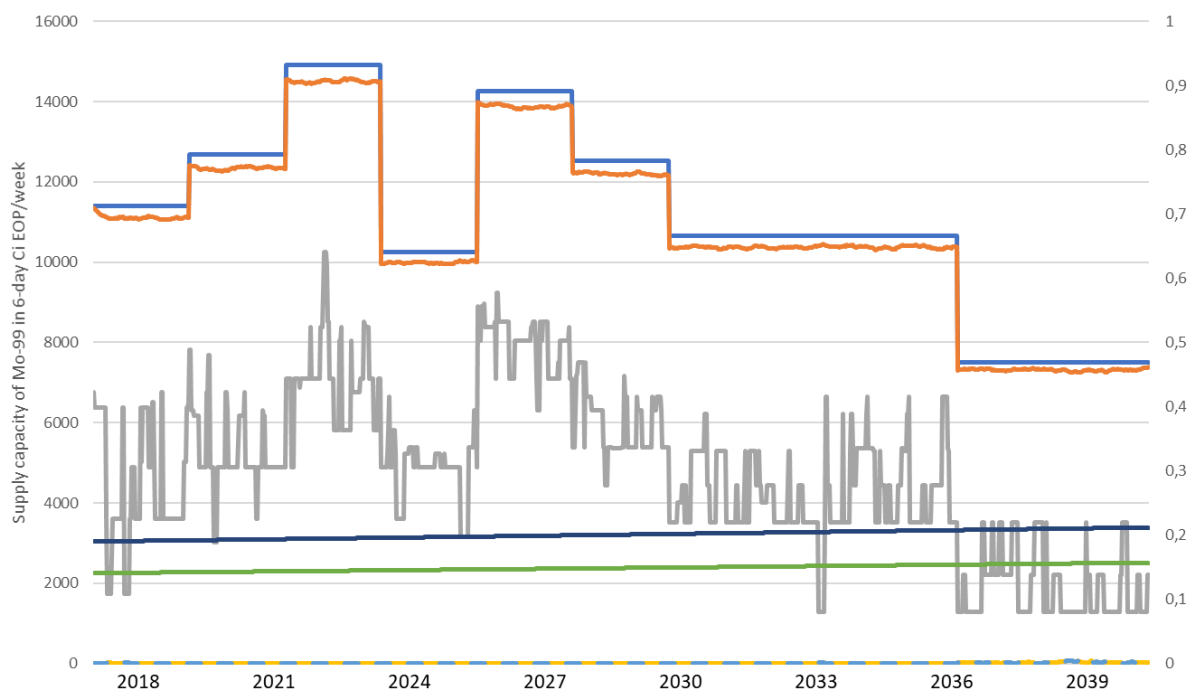
Nevertheless, neither from an irradiation point of view nor from a processing point of view any shortages are to be expected. The only bottleneck for achieving self-sustainability of the supply chain would be uranium enrichment and target production in Europe. As pointed out in section A.13.1, this is feasible but would require larger costs for enrichment and target production than currently is the case – and thus increased fuel and target prices. It was pointed out by the expert group that such an investment would be the only way of attaining a high degree of self-sustainability (as uranium mining would still be the bottleneck). The question whether the costs of self-sufficiency can be borne is a political one.

The investments associated with the construction of MYRRHA and PALLAS are €1.6 billion and €500 million respectively. PALLAS is mainly funded by commercial investors. MYRRHA requires investments from the Belgian government and from the ESFRI roadmap. The building of an LEU enrichment facility requires investments as well. Experts from the advisory board stress that EU-produced LEU would reduce the risk of new investments in irradiation and processing processes. Currently, conversion to 19,75% enriched LEU has been realised or is being realised by the main irradiators and processors in Europe under political pressure from the USA – although the need in terms of non-proliferation is also recognised in Europe. This conversion is associated with significant investments by irradiators and producers. Dependency on the USA could lead to political pressure to accept a further concentration decrease of U-235 in LEU fuel and targets and thus a new series of investments by irradiators and processors.

A.13.6.4. Reference scenario

At the suggestion of the expert group, a scenario in which only PALLAS was to be built would be considered more realistic. However, it was also deemed a **necessity** for

achieving self-sufficiency from an irradiator perspective. As HFR is currently a large international supplier, PALLAS would have to take over this position to secure supply for Europe. This scenario does not change anything with respect to processing capacity.



(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively– the yellow/light blue line indicates the probability of shortage (right axis)– the green line is demand, the dark blue line is demand + ORC). The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability

Figure 130 Reference **irradiator** scenario for **European** supply and demand.

The figure above clearly shows the closure of BR-2 in 2036 without replacement by MYRRHA. However, due to the existence of PALLAS, this would only lead to a slight increase in the probability of shortages (a chance of 1-2 per million). In the workshop the acceptability of such a risk was not discussed. It was stated by one of the experts that self-sustainable supply of molybdenum without PALLAS would not be possible. The results of the model were said to be in line with the results of other proprietary models on the market.

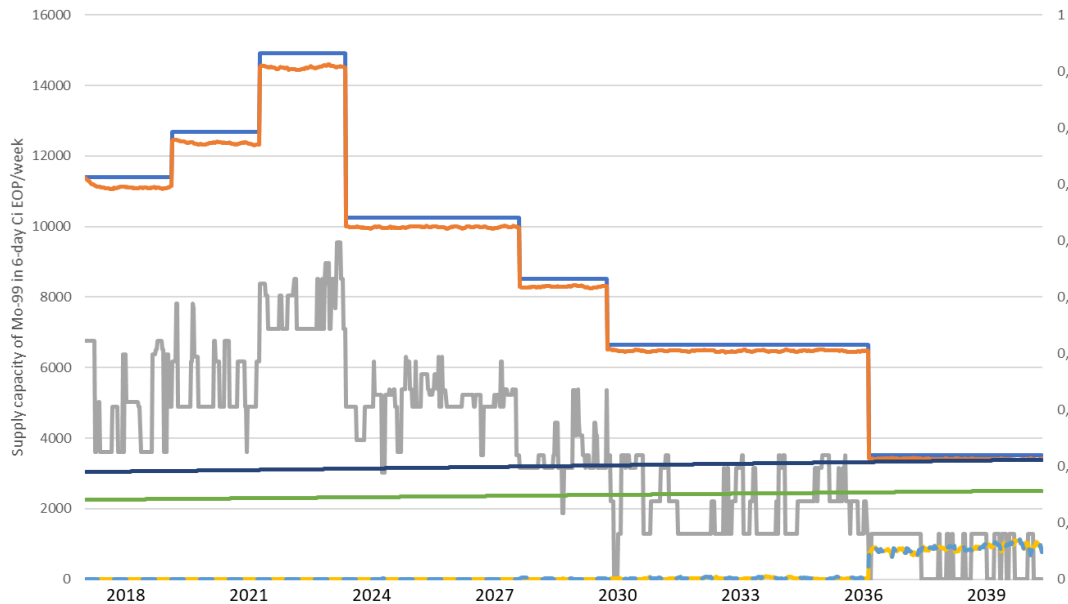
For this scenario to be realised, PALLAS needs to become reality. This is associated with an investment of approximately €500 million, mainly paid by commercial investors.

A.13.6.5. Mid-range scenario

In this scenario all of irradiators that are identified by the OECD NEA (2017 update) will be built and BR-2 will be extended until 2036 – without MYRRHA taking over the MR production afterwards and PALLAS being realised. The majority of the irradiators on the OECD NEA list are to be built outside Europe.

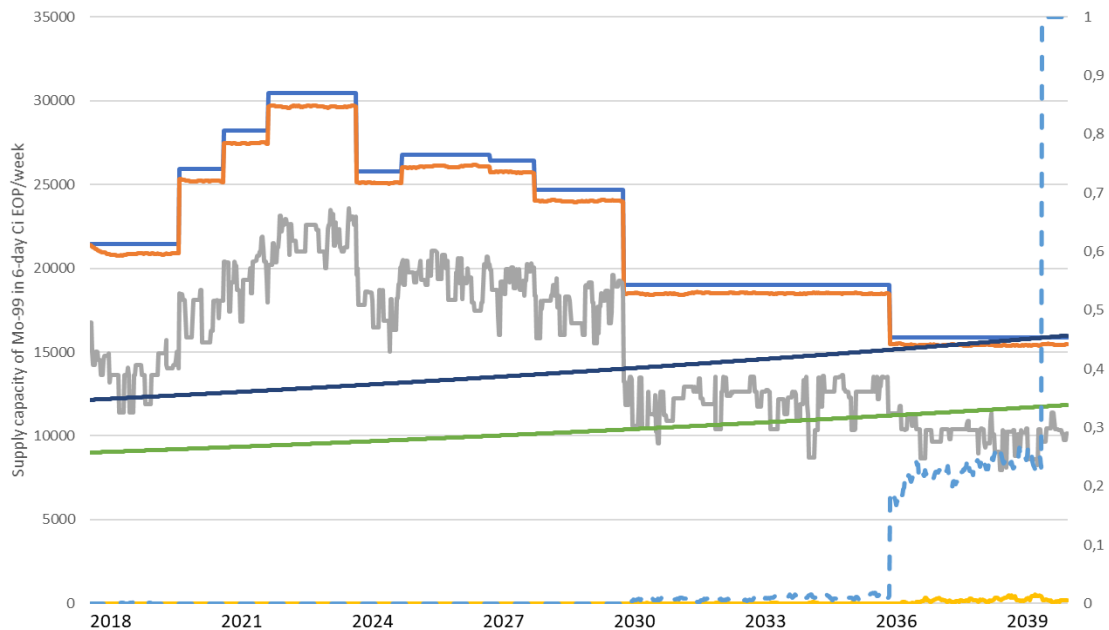
This scenario already leads to a small risk of EU-domestic shortages after 2030, with the planned shutdown of the LVR15, BR-2, and MARIA reactors. After the closure of BR-2 in 2036, the chances of shortage would reach 5-6%, with the +35% ORC demand curve for the EU coming close to the mean supply curve.

From a global perspective, the situation would be direr as the ORC threshold would be at 25% chance of shortages from 2036 onward and not be maintained at all in 2039. Again, this includes the 35% ORC safety margin – whether the breach of this margin is acceptable was not discussed in the workshop. The margin of 35% ORC is generally accepted and based on an historic analysis by OECD NEA.



(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively – the yellow/light blue line indicates the probability of shortage (right axis) – the green line is demand, the dark blue line is demand + ORC). The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability

Figure 131 Mid-range **irradiator** scenario for **European** supply and demand



(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively – the yellow/light blue line indicates the probability of shortage (right axis) – the green line is demand, the dark blue line is demand + ORC). The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability

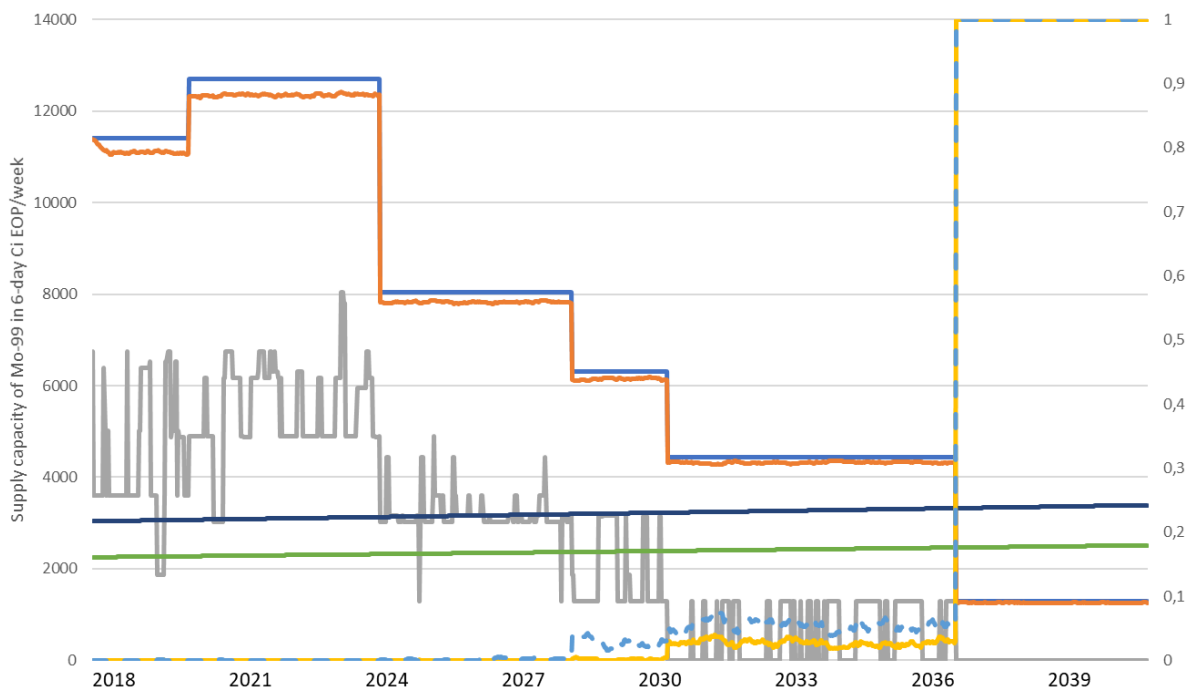
Figure 132 Mid-range **irradiator** scenario for **global** supply and demand

The processing capacity in this scenario is both globally as in the EU sufficient and does not differ from previous scenarios. In principle, there will be sufficient processing capacity to be self-sufficient in the EU.

The option of deploying cyclotrons as short-term solution to alleviate shortages was discussed shortly. Whereas cyclotrons indeed have a shorter construction time than reactors, such a solution would not be scalable in order to compensate for the loss of reactor capacity. Furthermore, as demonstrated in this report, the cost would be prohibitively high (although in cases of extreme shortage, such investments and costs could be overseen).

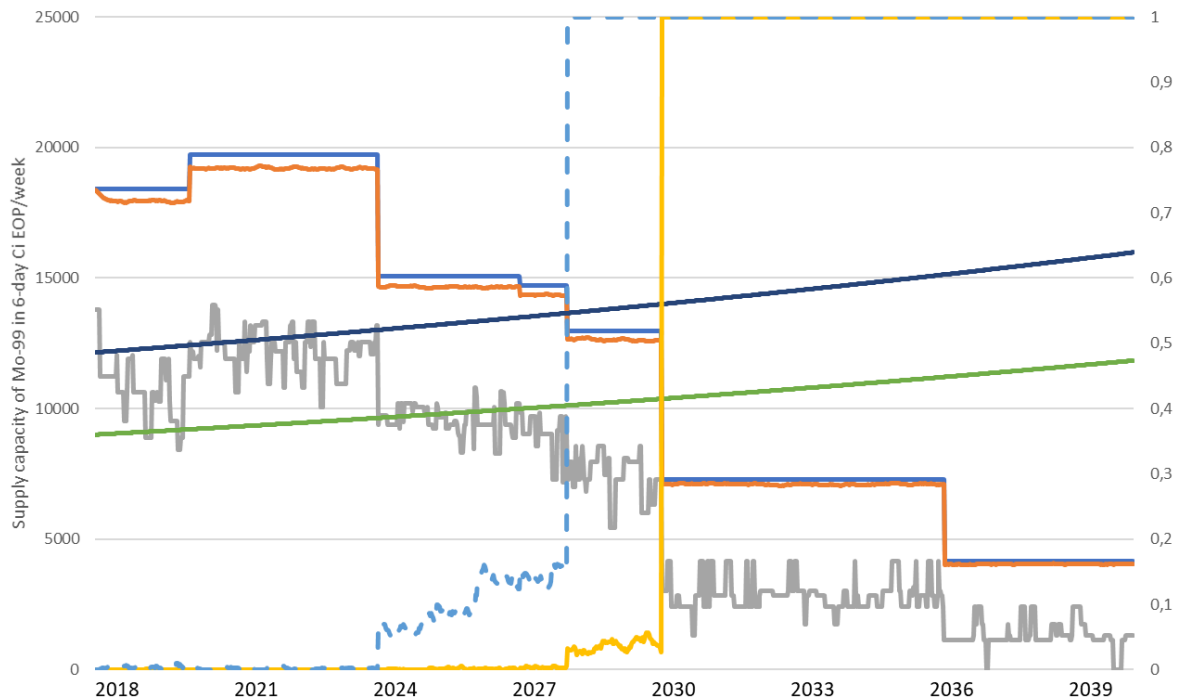
A.13.6.6. Conservative scenario

The conservative scenario only entails operating irradiators and those that are deemed certain to proceed. With the shutdown of HFR, the chance of shortages increases after 2024 – even when +35% ORC is not taken into account.



(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively – the yellow line indicates the probability of shortage, the light blue line + ORC (both right axis)– the green line is demand, the dark blue line is demand + ORC) The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability.

Figure 133 Conservative *irradiator* scenario for **European** supply and demand

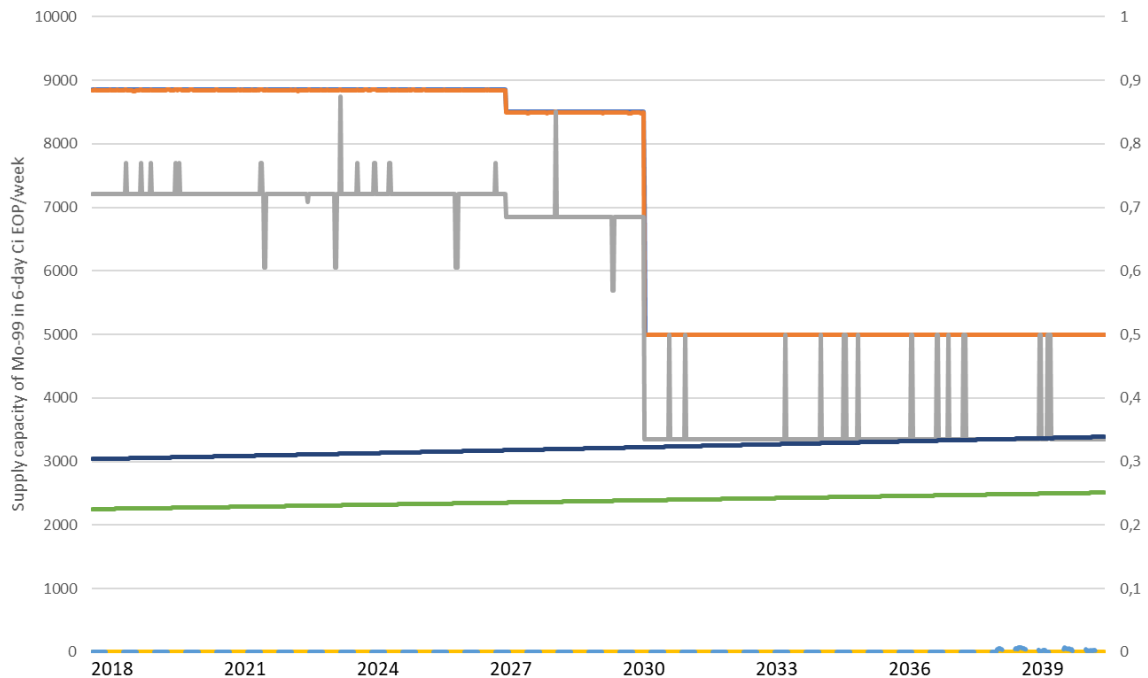


(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively – the yellow line indicates the probability of shortage, the light blue line + ORC (both right axis)– the green line is demand, the dark blue line is demand + ORC) The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability.

Figure 134 Conservative **irradiator** scenario for **global** supply and demand

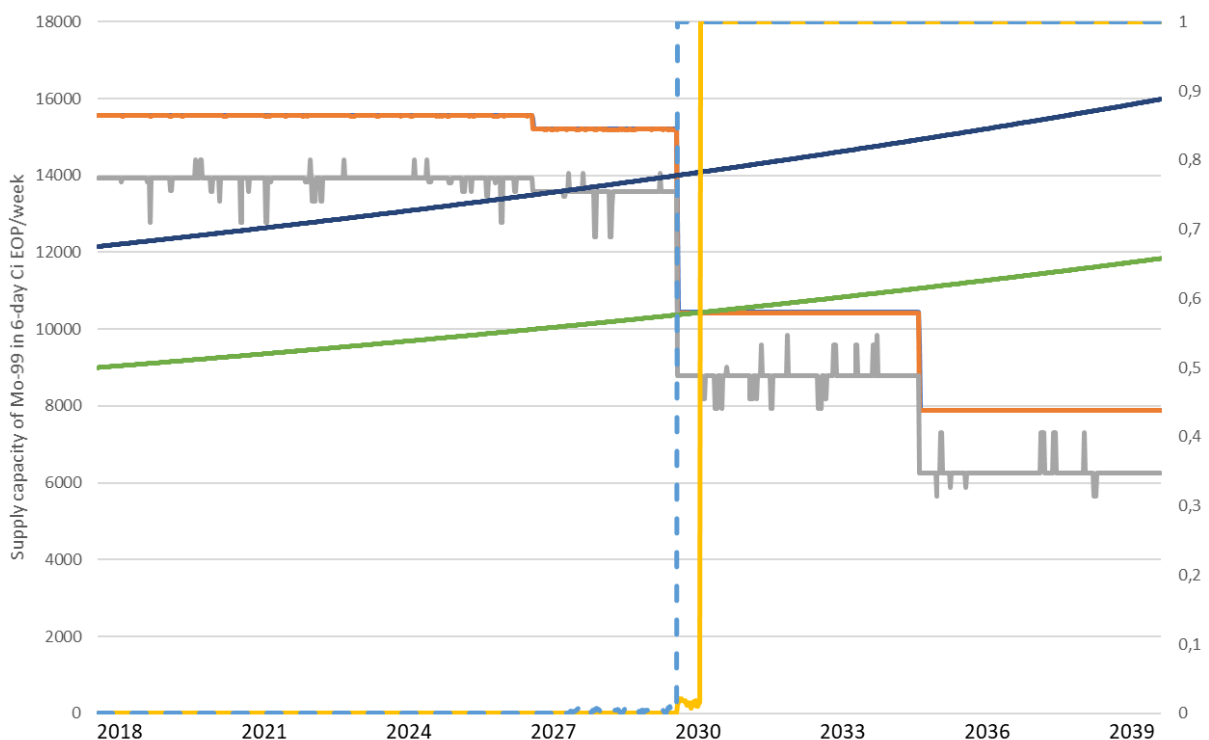
Globally, shortages would become visible from 2024 onward (see figure 134), while at a European level from 2028 onward with the closure of LVR-15 (see figure 133). The European situation would therefore not be resolved by supply from overseas. In 2036 there would definitely be a shortage in Europe and the world in this scenario with the closure of BR2. In that year the supply falls significantly below the expected demand, even without +35% ORC.

For processors this scenario also included only the currently operating facilities. In Europe, the current capacity is sufficient until 2038, where there is only a very small chance of shortages of about a few per million (max. 0.008%) if +35% ORC is considered. Globally, there are however shortages to be expected from 2027 (+35% ORC)/2030 onward. In the year 2030 there will be a definite shortage in processing capacity both with and without taking +35% ORC in account in this scenario – this shortage will remain from 2030 onward.



(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively – the yellow line indicates the probability of shortage, the light blue line + ORC (both right axis) – the green line is demand, the dark blue line is demand + ORC) The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability.

Figure 135 Conservative **processing** scenario for **European** supply and demand



(blue, orange and grey lines show production capacity maximum, mean, and minimum respectively – the yellow line indicates the probability of shortage, the light blue line + ORC (both right axis) – the green line is demand, the dark blue line is demand + ORC) The horizontal axis is in years, the left axis is 6d Ci EOP/week, the right axis is probability.

Figure 136 Conservative **processing** scenario for **global** supply and demand

This scenario was deemed rather unlikely by the expert group, although its occurrence could not be entirely ruled out.

A.13.6.7. Discussion

The expert group supported the different scenarios and the exercise performed to arrive at these scenarios. It was said to be in line with conclusions from other proprietary models available on the market. It was noted that price is a large determinant and that technological developments as well as price could significantly alter the demand landscape in a matter of 5-10 years. Therefore, any model outcomes beyond 2023-2028 are speculative and strongly subject to government and market actions taken in the (near) future. This was also identified earlier in this chapter.

As long as reactors are the main suppliers of molybdenum, the opening or closure/shutdown of a single facility has important ramifications for the worldwide supply chain. A market consisting of a small number of large producers is always more vulnerable than a market consisting a large number of small producers. Alternative model runs with slightly different demand curves are not significantly altered in this situation.

With respect to processing capacity, Europe seems to be self-sufficient on the long term. Although some notes could be made whether overall available capacity in Europe is a sufficient indicator for EU self-sufficiency, given limitations in geographical distance between irradiators and processors and the difference in targets and processes used. Worldwide, a shortage will appear after 2030 if no new processors will enter the market.

The expert group furthermore agreed that a mid-range scenario + PALLAS would be considered the *reference scenario* for this study. It was agreed that a supply situation without PALLAS (with a less relevant role in the context of Molybdenum supply for MYRRHA) would not lead to European self-sufficiency and could create shortages at the global scale.

A.13.7. Conclusion on Mo-99

Our expert group, expert interviews and literature review confirm that it is very difficult to get reliable figures concerning the future demand and supply of Mo-99. Our own survey data supports the general notions of existing studies regarding demand development but does not improve the existing level of detail.

The current demand for Mo-99/Tc-99m activity in EU28 is not easily estimated due to limited availability of reliable data sources. Two routes have been explored to estimate the current demand for Mo-99/Tc-99m in EU28. The first resulted in a demand for Mo-99 activity of 1.980-2.250 6-day Ci EOP/week. The second resulted in a demand for injected Tc-99m activity of $1 \cdot 10^3$ Ci/week.

Supply is mainly determined by the availability of reactors whose funding and actual realisation remain uncertain. Alternative Mo-99 production processes are more expensive or at an earlier stage of technological development than tried and tested reactor solutions. Furthermore, given the capacity of most alternatives, a concerted deployment of local solutions would have to take place to reach same production capacity as one reactor. Nevertheless, given the shorter construction times, alternatives such as cyclotrons might present a solution to foreseen shortages in the mid-term.

We confirm the conclusion of market analysts, AIPES and the European Observatory, that the use of Mo-99/Tc-99m will remain stable in Europe until 2030. In the longer term, demand may decrease in Europe, but this is highly dependent on technological developments in terms of quality and costs. The characteristics and the evolution of the radioisotopes theranostic market suggest that, despite the PET share increase, SPECT Tc-99m remains the major imaging technique.

The goal of full European self-sufficiency is very ambitious and can only be met under very favourable conditions (optimistic scenario). The EU is largely dependent on the US for the production of LEU fuel but could diversify supply by importing more LEU from Russia. If European self-sufficiency is the ultimate goal, the EU should invest or support investment in a LEU enrichment facility – for up to 19,75% enrichment – and associated chemical conversion facilities. The realisation of these facilities would require significant investments. EU produced LEU from enrichment will have a higher price than the currently US imported LEU from diluted stock piles – complicating FCR discussions.

In the conservative scenario, the shutdown of HFR would lead to EU-domestic shortages in 2024, whereas in the mid-range scenario, the shutdown of BR-2, MARIA and LVR15 would lead to EU-domestic shortages in 2030 as alternative irradiators are to be built outside Europe. For achieving European self-sustainability in the longer term, the irradiation capacity of PALLAS (and/or MYRRHA) would be required.

A policy focus on Mo-99 availability remains important: developments on the supply side should be regularly monitored, but especially more insight is required for the demand side. A regular update of the presented numbers and scenarios would be required.

A14. Alternative radioisotopes production projects status

New production means development projects exist, namely in Canada and in the USA, which is the major Mo-99 world market (around 50%) and where mass-production facilities are not yet available.

In Canada, the option seems to rely on a network of cyclotrons for Mo-99 production. In addition to the cost issue (Mo-99 production in cyclotrons will have much higher cost than reactor-produced one), the question regarding the production means for all the other isotopes remains open.

These projects and their status are depicted below³⁷⁴.

A.14.1. 2016 situation

Technologies	NNSA-Supported Domestic Mo-99 Production Projects						Other Potential Domestic Mo-99 Production Projects						
	NorthStar (n, γ)	NorthStar (γ, n)	SHINE	GAMMUR Nordion	B&W	GE-Hitachi	Coqui RP	Eden RI	Filibe Energy	PermaFix	Niowave	NuView	NWMI
Target Material	Mo-98 (nat/enr)	Mo-100 (enr)	LEU	LEU	LEU	Mo-98 - nat)	LEU	LEU	LEU		LEU		LEU
Target Type	Metal disk	Metal disk He cooled	UO2SO4 solution	UO2 pellets	U solution	Metal	Plate	solid reactor/fuel target	UF4 solution				
Mo-99 production reaction	Neutron capture (reactor)	Photon induced (e-beam accelerator)	U fission (ADS)	Neutron capture	Neutron capture (solution reactor)	Neutron capture power reactor	Neutron capture (reactor)	Neutron capture (reactor)	Reactor with liquid-fluoride thorium fuel		similar to Shine		Neutron capture (reactor)
Mo-99 recovery method	Aqueous dissolution	Aqueous dissolution	Titania column + mod. Cintchem	Reactive gas extraction	ion exchange	Aqueous dissolution	Aqueous dissolution	Aqueous dissolution	Proprietary		Aqueous dissolution		Aqueous dissolution
Recycling	Y	Y	Y		Y				Y				Y
Mo-99 specific activity	Low (1-10 Ci/g)	Low (1-10 Ci/g)	High	High	High	Low	High	High	High		High		High
Questions	Low activity -> New generator necessary (Radiogenix, investment ?) Targets recycling. Enr Mo sourcing.		Tritium, H2, 14 MeV neutrons	Nordion exit project (04/18)	Project Suspended	Project Suspended	Not yet funded	Looking for funds	Exotic design				
NNSA Support	25 M\$	5 M\$	15 M\$										

Figure 137: US projects description

As of 2016, about 13 projects had been put in perspective. The projects that were deemed most promising are supported by US NNSA.

The next table summarizes the diverse steps a production mean must go through before the product reaches the marketplace. This table shows that all US projects had yet in 2016 major (and costly) drawbacks to overcome before they could compete with the existing, Research reactor-based, proven supply chain.

³⁷⁴From "Molybdenum-99 for medical imaging".US National Academy of Sciences. 2016.

MATURITY STATUS		NNSA-Supported Domestic Mo-99 Production Projects						Other Potential Domestic Mo-99 Production Projects						
		NorthStar (n, y)	NorthStar (y, n)	SHINE	GA	B&W	GE-Hitachi	Coquir RP	Eden RI	Filbe Energy	PermaFix	Niowave	NuView	NWMI
Has production technology been demonstrated ? A: Yes, at commercial scale/B: Yes, at pilot scale/C: Yes at bench scale/D: No	Are production facilities available ? A: All needed facilities available/B: Some needed facilities available/ C: Some pilot facilities available/ D: No facilities available	A	C	Ba	C			A	A	D	B	C	A	A
														D (targets)
Are target materials available ? A: Available from multiple suppliers/B: Available from a single government/C: Available from a single commercial supplier/D: No readily available	Irradiation Processing	A	D	C	A	D	A	D	D	D	N/A	B	A	B
		B	D	C	A	D	B	D	D	D	D	unknown	D	
[Type of target]	Are target materials available ? A: Available from multiple suppliers/B: Available from a single government/C: Available from a single commercial supplier/D: No readily available	A (natural)	A (natural)	B	B	B	B	B	B	B	N/A	B	B	B
		C (enriched)	C (enriched)											
Is the product (Mo-99, T c-99m) compatible in the existing supply chain ? A: Product compatible/B: Product partially compatible/ C: Product incompatible	Irradiation Processing	[Mo-98]	[Mo-100]	[LEU]	[LEU]	[LEU]	[Mo-98]	LEU	LEU	LFT a	N/Ab	LEU	Mo-98	LEU
		B	B	A	A	A	B	A	A	A	A	B	A	
Have regulatory approvals for facilities been obtained? A: Approval for operations/B: Approval for construction/C: Approval for testing/D: No Approvals	Irradiation Processing	A	D _b	B	C	D	D	D	D	D	N/A	A	D	A
		B	B	B	A _c	D	D	D	D	?	D	D	D	D
Have regulatory approvals for products (Mo-99, Tc-99m) been obtained ? A: ANDA/sANDA/NDAs/NDAs approved/B: ANDA/sANDA/NDAs/NDAs in development with additional information requested/C: ANDA/sANDA/NDAs/NDAs submitted with no addial information requested/D: No ANDA/sANDA/NDAs/NDAs	Irradiation Processing	B	D	D	D	D	D	D	D	D	D	D	D	D
What is the committee's estimated timescale for bringing products to the market place ? A: Before 2016/B: Between November 2016 and March 2018/C: After March 2018/D: Project suspended	Irradiation Processing	B	C	C	C	D	D	C	C	C	C	C	D	C

source : MOLYBDENUM-99 FOR MEDICAL IMAGING/ US National Academy of Sciences 2016

Figure 138: Maturity Status of new Mo-99 production projects

A.14.2. 2018 update

In 2016, the closest to completion project was the NorthStar (n,γ) project based on a research reactor (MURR).

This process uses Mo-98 targets and works, even if some problems remain to be solved: enriched Mo-98 targets sourcing must be secured and manufacturing and reprocessing must be industrialized, unless Mo-99 mass-production yields shall remain poor.

The low specific activity of the targets necessitates a new generator design, called Radiogenix®. This rather big machine, as compared to a standard Tc-99m generators, necessitates an investment from the radiopharmacies. This may be possible in the centralized US radiopharmacies but would be difficult for European hospital radiopharmacies. Using this machine necessitates also a FDA authorization.

The corresponding New Drug Application (NDA) was filed for Radiogenix® early 2013. The FDA authorization has just been granted (8/2/2018). Nevertheless, this authorization requires additional studies and reports submission³⁷⁵

- Evaluate the fluid path bioburden and final product endotoxins and sterility in the RadioGenix™ System at interim timepoints and the System expiry from diverse clinical sites. Deadline: March 2020.
- NorthStar will perform studies to evaluate effectiveness of radiolabelling all commercially available technetium Tc 99m drug product kits in the US (except the ones already evaluated in NDA 202158), as per kit manufacturer's directions using representative sodium pertechnetate Tc 99m injection solutions obtained from three different RadioGenix™ Systems. The studies for each kit will cover different volumes (from low to high end range) of sodium pertechnetate Tc 99m injection solutions obtained throughout the 14-day shelf life of the potassium molybdate Mo 99 source. The effectiveness study must verify that the radio-labelled kits meet the quality requirement listed in the kit manufacturer's package insert. Deadline: mid 2019
- During the annual maintenance check of each of 10 systems: 1. Identify and report all locations of occlusion, clog or deposit build-up in the fluid lines including the valves. 2. Identify and report all locations of leaks in the system. 3. Report any elution radioactivity yields which are out of tolerance from the estimate provided by the software. 4. Report any elution volumes which are out of tolerance. Deadline: April 2020

Other US projects also experienced some progress:

- For the Shine project, the civil works of the "Building One" are finished. Buildout inside the building is starting and during summer 2018 the facility will be used to house the "first integrated, full-size SHINE production system", which seems to be essentially a pilot/demonstration facility aimed to answer the numerous open technical questions³⁷⁶ relative to this new design. During the future construction of SHINE's main production facility, Building One will be used to train employees and

³⁷⁵ NDA 202158. Letter from FDA to Northstar dated 8/2/2018

³⁷⁶ See US NRC Safety Evaluation Report of Shine (2016)

develop operating history with equipment. Going forward, Building One will be a state-of-the-art technology development centre.

- BWX Technologies, Inc. (which suspended its own Mo-99 production project) just announced (17/4/2018) that it has signed a definitive agreement to acquire Sotera Health's Nordion medical radioisotope business. "The acquisition accelerates and de-risks BWXT's entry into the medical radioisotope market by adding licensed infrastructure, approximately 150 highly trained and experienced personnel, and two production centres to BWXT". However, this also implies that Nordion exited the GA/MURR project. Consequences on this latter project are unknown.
- In addition, BWXT announced in June 2018 that they are developing another Mo-99 project using the CANDU Darlington station. As neutron fluxes in CANDU are rather low, this necessitates also a specific generator development. This will add to the timeframe necessary for industrializing the process.

Hence, even for the most advanced projects, it seems that it may yet take time before industrial production takes place in the USA.

A15. Industrial/Research applications developments

A.15.1. APAE Key-Recommendations per domain

In its final report³⁷⁷, APAE issues a series of detailed recommendations for developing the accelerators applications to the Health, Energy, Industry, Security and Research domains.

APPLICATIONS OF PARTICLE ACCELERATORS TO HEALTH

Radiotherapies

The key recommendations for funding are:

- Further research in medical physics and the promotion of technological development in the field of radiotherapy using a multidisciplinary approach, including the use of biological information (genetic and molecular biology-based data) and immunological protocols, clinically oriented towards personalised medicine, with the participation of clinical centres, academics, laboratories and industry (including physicians, physicists, biologists, engineers and paramedical staff).
- Strong links and cooperation between academics, industry, national and international research organisations such as CERN, public and private hospitals, universities, with the widespread dissemination of results to the community;
- A design study for a future multi-particle therapy facility, possibly including helium-ion treatment and/or secondary imaging as its primary goals;
- Clinical studies to demonstrate the benefits of new therapies;
- The establishment of systematic RBE experiments in Europe, including in-vivo animal studies;
- The study of solutions for ion secondary-particle imaging and other dose delivery instrumentation;
- A programme of development for high-gradient ion acceleration;
- Support for the development of rotatable superconducting magnet systems.
- Studies to reduce significantly both the initial investment and the functional costs of radiotherapy systems.

Radionuclide production

- The investigation of alternative mechanisms for Mo-99 and Tc-99m production in Europe.
- The further development of compact sources for PET radionuclide production directly in hospital, in particular for the use of the shorter half-life radioisotopes.
- The study of novel radionuclides for therapy in particular, but also for imaging.
- The development of compact, high-current accelerators with the ability to accelerate and extract different types of particle for the production of radionuclides for therapy and imaging.

APPLICATIONS OF ACCELERATORS TO INDUSTRY

Very low-energy e-beams

The view from industry and research organisations in order of priority is:

- Invest in R&D by offering suitable support programmes for technology development.

³⁷⁷Applications of Particle Accelerators in Europe (APAE) Final Report. 2017

- Invest in the development of the next generation of e-beam technologies, including peripheral components, such as high-voltage power supplies, to create more compact, more robust systems for industrial use – that is, systems that are easy to handle, ready for Industry 4.0, and cheap and simple for manufacturing low-level products.
- Lobby for the updating of laws with respect to the specialities of very low energy electron irradiation.
- Lobby for the updating of laws regarding food irradiation.
- Invest in basic education and training in the area of electron-beam technologies and its diverse applications and possibilities.

Low-energy electron beams

- There is a need for strong programmes supported by the governments to move e-beam technology from the laboratory to industry.
- There is a need to strengthen the connections between end-users and suppliers. The ARIES H2020 project can play a pivotal role in achieving this aim.
- There is a growing use of low-energy e-beam accelerators for the curing of inks, coatings and adhesives.
- Many existing applications require accelerators with powers of tens of kW, but with lower costs, higher efficiency, and simpler operation. The evolution of existing industrial accelerators can improve performance, reliability, efficiency, and lower costs to some extent.
- There are many emerging and exciting applications that need a higher beam power and efficiency to make them commercially viable. Some require very high power (MW class) and high energy (5 to 10 MeV) with high wall plug efficiencies.
- The wider geographical deployment of established applications, such as tyre rubber crosslinking, the surface treatment of seed for agriculture, municipal waste water treatment and other applications, needs to be encouraged.
- There is a growing need for mobile e-beam facilities for different applications: industrial waste water treatment, seed disinfestation, environmental remediation, etc.
- Small e-beam facilities including mobile accelerators are needed to develop applications.
- Large government/EU spending on big science accelerators drives the majority of advanced accelerator R&D worldwide. Industrial accelerator builders are often not well connected to these efforts. The US, Europe and China are now encouraging such connections. Programmes are required.
- Revolutionary accelerator systems based on new technologies, like superconducting RF (SRF) and improved RF systems developed for big science accelerators, may provide a path to very high-power, high-efficiency accelerators with significantly smaller capital and operating cost, and of substantially reduced size.
- The international collaboration between EU institutions and programmes, IAEA and other bodies around the world is a key factor in connecting industrial accelerator groups, research facilities and radiation chemistry laboratories, and enhancing technology transfer, both in accelerator construction and applications.

Ion beams

- Areas in which the potential of ion beams for the analysis and modification of materials has not been fully exploited or promises to be further exploited should be identified.
- It is important to identify what is strategically interesting and propose it to industry, and with that to show the politicians that ion beams provide industry with

commercial value.

- In the application to environmental pollution problems, it is important to remember that nuclear techniques provide only part of the desired information with regard to chemical composition. PIXE practitioners should not limit themselves to PIXE and IBA analyses in general, but try to diversify their activities by also carrying out other chemical and/or physical and optical measurements, and by establishing collaborations with other groups (such as chemists, geologists and physicists).
- In the application to cultural heritage, IBA techniques must focus on non-destructive, high-sensitivity, depth-resolved, quantitative analysis (covering the whole range of elements) of movable cultural heritage objects, to address specific case studies, and maybe provide molecular information as well, whereas portable/transportable and cheaper ED-XRF systems should be routinely used to provide qualitative information for restoration and academic study.
- Although IBA is considered to be non-destructive, since no sampling is needed, the irradiation may cause visible or non-visible, reversible or irreversible changes, depending on the material and the experimental parameters. This might pose a problem in the analysis of cultural heritage objects. An obvious mitigation strategy could be to decrease the beam current and the duration of irradiation. To do that, efficient detector systems, for example, based on arrays of detectors, are required.
- Outreach material (leaflets, publications) should be produced to provide information to environmental protection agencies, industry, archaeologists and curators on what they can expect from the use of accelerator-based nuclear techniques. For instance, environmental studies are a success story of IBA, having led to a high level of understanding of pollution generation and its dynamics; research has often motivated regulatory decisions, which have benefited the health of tens of millions of people. The modification of materials by ion beams also has a strong societal impact, but it is not easy to communicate; the opportunity for development depends on EU energy policy and energy management organisation.
- Access to ion-beam techniques needs to be facilitated. In the field of cultural heritage science, the access to nuclear physics techniques is not always straightforward. Currently, the IPERION CH (www.iperionch.eu) provides transnational access, free of charge, to large-scale facilities in France (AGLAE, SOLEIL) and Hungary (BNC, MTA Atomki) for users in the field. Nevertheless, these techniques are still not as well-known as they should be. A unique opportunity emerges, with the acceptance of the E-RIHS (European Research Infrastructure on Heritage Science) initiative for the ESFRI Roadmap. E-RIHS will provide state-of-the-art tools and services to the multidisciplinary communities of researchers working to advance knowledge about heritage and strategies for preservation.

APPLICATIONS OF PARTICLE ACCELERATORS TO ENERGY

MYRRHA and IFMIF are two key facilities able to better assess what the future of nuclear energy in the world could be. The EURATOM community should therefore grasp every opportunity to achieve the construction of these facilities.

As far as specific accelerator developments are concerned, clearly the priority areas of investment should be R&D activities on:

- The development of high-intensity high-reliability proton and deuteron beam injectors.
- The development of superconducting RF-cavity technology in a high-power, high-reliability context.
- The investigation of high-current beam dynamics and beam halos.

- The development of innovative beam instrumentation.
- The modelling of the reliability of particle accelerators.
- Safety studies of high-energy, high-current proton accelerators and their coupling to a spallation target.

APPLICATIONS OF PARTICLE ACCELERATORS FOR SECURITY

In the short term, high priority should be given to the development of:

- 3D imaging;
- automated image recognition;
- accelerators that support enhanced techniques, such as nuclear resonance fluorescence, to discriminate illegal cargo from legitimate goods.

These areas aim to decrease the time required for inspection in areas of high-traffic by providing operators with more information or by pre-selecting cargo to be inspected. This will likely increase throughput at ports and increase detection rates.

In the medium term, a priority area for investment would be the development of single-energy X-ray sources, which would allow the improved operation of accelerators in nuclear resonance fluorescence and active nuclear detection, as current X-ray sources produce a large spread in X-ray energy.

A significant long-term priority would be to take novel compact, high-performance accelerator technology, such as could be offered by laser or terahertz techniques, for example, from the laboratory into the security environment. These accelerators potentially offer a dramatic reduction in the size and weight of current security linacs, although significant development is needed to see if this can be achieved in a suitable environment.

APPLICATIONS OF PARTICLE ACCELERATORS TO PHOTON SOURCES

Accelerator-based photon sources have developed enormously over the past 50 years. If this pace of development is to continue, then it will be important to continue R&D in many of the disciplines of accelerator physics. Quite apart from the R&D required in more exotic areas such as laser-plasma acceleration, many of the more 'traditional' technologies would benefit from further development.

These include the following:

- High-brightness electron guns with a high repetition rate are needed (for longer duty-cycle FELs).
- The development of superconducting cavities with strong higher-order-mode damping will be needed for ERLs to operate at high current without suffering from instabilities.
- Improved modelling and simulation of low-emittance electron-beam transport from the source through to the undulator are needed to enable the design of linac-based sources to be improved.
- improvements of undulators operating in-vacuum, and of superconducting undulators with shorter period lengths than those available today, would be highly beneficial for both circular and linear machines.
- The development of new RF power sources will be needed as electronic vacuum tubes disappear from the market.

If such developments are to be possible, it will be necessary for laboratories operating synchrotron-radiation sources to continue to invest in healthy accelerator physics R&D programmes. Cooperation between these laboratories is also important. The European

SR community already meets annually to share operational experience of its facilities and to discuss new developments in the field. Many laboratories already collaborate through programmes funded by the EU. Stronger collaboration is recommended, as this can only be beneficial for all concerned. At the time of writing, the synchrotron radiation community has formed the LEAPS collaboration to seek further support from the EU.

APPLICATIONS OF PARTICLE ACCELERATORS TO NEUTRON SOURCES

Political processes:

A European roadmap is needed for the construction of new spallation sources and compact neutron sources, as well as the upgrade or replacement of existing sources. Furthermore, the neutron facilities must in the future invest in accelerator R&D and cannot depend on particle and nuclear physics to carry most of that cost.

High priority technical R&D is needed on:

- energy-efficient RF sources;
- high-power RFQs;
- new low-loss injection schemes and 'longer-pulse' extraction schemes for synchrotrons;
- high-quality superconducting RF cavities;
- cheaper, more efficient and more reliable superconducting and normal conducting accelerating structures and accelerator systems.

A.15.2. Outcomes of the US DOE workshop on accelerators

It is worth noting that these European recommendations are fully coherent with those issued after an USDOE workshop³⁷⁸, which are technically detailed in §12.3 below and summarized here. Focusing on energy and environment (E&E) accelerator applications, the US DOE organized this workshop to identify the R&D needs in order to foster new accelerator applications. One of the major goals of the workshop was to document in detail a complete picture of the landscape for potential E&E applications of accelerator technology as well as the synergistic effects of technological developments in the accelerator domain. The participants of this workshop identified a broad spectrum of research needs to move electron beam and superconducting technology from an innovative technology to one that is truly disruptive in the environmental and energy marketplace.

The application domains investigated are depicted below.

³⁷⁸ Workshop on Energy and Environmental Applications of Accelerators (June 24–26, 2015). US DOE, Office of Science. 2015.

Applications of Electron Beam Technology	
Treatment of water and wastewater	Radiation processing to purify and decontaminate water
Treatment of flue gas	Radiation processing to purify gas streams
Treatment of sewage sludge	Radiation processing to decontaminate sewage sludge
Environmental remediation of hydrocarbon contaminated soils	Radiation processing of hydrocarbons to make contaminated soil more amenable to other remediation techniques
Medical waste sterilization	Radiation processing to decontaminate medical waste
Conversion of fossil fuels	Conversion of fossil fuels by radiation processing
Asphalt treatment	Improving wear-resistance and weather-resistance of asphalt via irradiation
Applications of Superconducting System	
Superconducting wind generators	More compact and efficient wind generators through use of superconductors
Magnetic separation	Separation in industrial flow streams with high magnetic fields
Electrical grid technologies	Superconducting power transmission and load-leveling

Table 52 : Applications of e-Beams technologies in the USA

The basic impediments to deployment of accelerator-related technology identified by the DOE workshop participants are:

- i. lack of availability of accelerator systems that meet the required performance levels for full-scale industrial application, which are typically a factor of ten or more beyond today's state of the art,
- ii. the need for accelerator systems that are both highly efficient and reliable, economically competitive with incumbent technologies, and
- iii. lack of pilot-scale applications of these new technologies to demonstrate their efficacy and performance.

More in detail, the application needs are summarized in the figure below.

		Energy and environment applications						
		Wastewater	Sludge	Flue Gas	Medical waste	Environmental Remediation	Asphalt treatment	Emerging applications
Capabilities	Demo/pilot scale 0.5 MW; 0.5-1.5 MeV	1	2	2	1	1	3	1
	MW-class DC system 1 MW; 1-2 MeV	1	2	1	2	2	2	1
	MW-class high-energy 1 MW; 10 MeV	2	1	3	1	1	1	1
	Ten MW-class high-energy 10 MW; 10 MeV	2	1	3	3	1	1	1

1	Very important
2	Somewhat important
3	Not important or not applicable

Table 53 : Technological needs according to US DOE workshop

The table below summarizes the technical gaps in the present state-of-the-art of electron-beam accelerator technology and the required R&D activities needed to bridge those gaps. The accelerator capability targets shown below meet the needs pictured in the figure above.

	Demo/ Small Scale	Medium Scale Low Energy	Medium Scale High Energy	Large Scale High Energy
Description	Demo and pilot-scale low-energy systems	MW-class, industrial-scale, low-energy systems based on DC technology	MW-class, industrial-scale, high-energy systems	10 MW-class, industrial-scale systems based on RF technology
Applicability to Environment & Energy Needs	Sterilization, R&D	Flue gas, wastewater	Wastewater, sludge, medical waste	Wastewater, sludge, medical waste
Electron Beam Energy	0.5–1.5 MeV	1–2 MeV	10 MeV	10 MeV
Electron Beam Power	>0.5 MW	>1 MW	>1 MW	>10 MW
Electron Beam Current	0.33–1.0 A	0.5–1.0 A	0.1 A	1 A
Target Capital Costs	<\$10/W	<\$10/W	<\$10/W	<\$5/W
Target Electrical Efficiency	> 50%	> 50%	> 50%	>75%
Size Constraints	None	Some applications require portability	Some applications require portability	Compact designs drive down overall CAPEX since shielded enclosures are major expenses

Yellow highlighted columns : need approximately one order of magnitude improvements beyond the capabilities available today

Table 54 : Technical gaps evaluation and R&D needed (US DOE workshop)

Summary of Findings and Research Needs

The identified basic research needs are summarized below in terms of (i) immediate science-based needs (i.e., discovery research and use-inspired basic research) and (ii) synergistic application-side needs. Because of the broad scope of applications considered, and the diversity of workshop attendees, the resultant list of research needs was wide-ranging and, in many cases, overlapping between applications.

1 Immediate (Near-Term) Science-Based Research Needs

Applications of Electron Beams

- Develop the science needed to evaluate and define E&E accelerator applications to overcome short-term show stoppers.
- Conduct basic research to develop a fundamental understanding of the effect of electron beam technology on the “Grand Challenge of Sustainable Environmental and Energy Applications.”

Accelerator Technology

- Advance technologies to overcome limitations in high power electron beams:
 - o Improve reliability, beam power, and performance of DC accelerator systems.
 - o Optimize linear accelerator systems for low-energy, high-beam power operation.
 - o Understand and overcome beam dynamics limitations of ampere-class beams in the 1–10 MeV range.
 - o Develop more reliable and efficient RF power sources and delivery systems suitable for >1 MW applications.
- Develop electron beam technology to extend the beam power reach by more than one order of magnitude beyond today’s capabilities at 1 and 10 MeV.

Electron Beam Systems Engineering

- Develop science-based predictive models of the total energy footprint for new electron beam systems.
- Develop predictive science-based models to optimize new electron-beam system geometries, considering accelerator voltage, current, vacuum containment, and shielding materials.

Radiation Chemistry and Irradiation Studies

- Develop science-based predictive models to understand radical yield from irradiated aqueous streams as modified by environmental parameters.
- Develop predictive science-based models of fundamental changes in wastewater due to electron beam irradiation.
- Develop focused science-based predictive models of medical (hospital) waste sterilization to allow landfilling. Unique cost/energy advantages of electron beam technology will aid to overcome short-term show stoppers.
- Gain fundamental understanding of the chemistry of electron beam irradiation of hydrocarbons in the environment.
- Gain fundamental understanding of advanced, real-time, in-situ imaging concepts to optimize electron dose distribution in mixed-density, non-aqueous wastes.

Superconducting Systems

- Gain fundamental understanding of the operation of high temperature superconducting coils in the temperature range between boiling liquid helium and liquid nitrogen.
- Develop a basic understanding of stability, quench, and other origins of magnet failure when operated at temperatures above 10 K.
- Gain understanding and demonstrate cryogen-free magnet systems.
- Develop magnet coils based on high temperature superconductors.
- Conduct R&D on SiC devices for advanced power supplies/converters.
- Conduct R&D on lowering the cost of flexible, long-length cryostats with minimal heat leak and develop efficient cooling methods for cooling below liquid nitrogen temperatures.
- Gain fundamental understanding of conductor performance and properties above 4 K.
- Coordinate, leverage, and work with researchers in other programs pursuing synergistic R&D.

2. Synergistic and Applied Research (Longer Term)

- Develop complete electron beam systems that demonstrate higher beam power with reduced capital costs, increased reliability, and improved efficiency.
- Demonstrate proof of technology at large scale in actual environmental application in conjunction with major potential users and societies.
- Develop training formats and educational programmes on electron beam applications for the environmental engineering profession.
- Launch focused programme to build and test magnets in the 10–60 K, 2–8 T range.

To conclude, accelerator-based applications seem to have a bright future globally provided significant technical and economic improvements are made. APAE has described the needs clearly, which have been confirmed by US experts. The question is to know how the EC could support these needs. See the Challenges in Research chapter above.

A16. Safety questionnaire

The Blank Questionnaire sent to Research Reactors is given hereafter

Foreword

The purpose of this questionnaire is to gather information to support European Commission SAMIRA initiative (*Strategic Agenda for Medical, Industrial and Research Applications of nuclear and radiation technology*). The current status of European Research Reactor (RR) Safety is being investigated by EC, in their importance among the Tc-99m supply chain.

Questionnaire

Research Reactor Characteristics

Name of the Research Reactor	
First Criticality Year of the installation	(Year)
List the main RI produced on a regular basis	☐ Mo-99 ☐ I-131 ☐ I-125 ☐ (to be completed) ☐ (to be completed) ☐ (to be completed)
Mo-99 peak Weekly Prod. Capacity (<i>in Ci EOI for current and future evolutions if any</i>)	(Ci EOI)
Mo-99 average production weeks per year	(1 – 52 weeks)

Long-Term Operation (LTO)

Expected Design Lifetime (if any)	(Nb of Years)
Expected final shutdown date (if any)	(Year)
Until which date the Operating License of the installation is valid?	(Year)
Do you plan to extend the life of the installation? For which duration?	☐ Yes, for ___ years or until 20___ ☐ No
If you already launched a long-term operation program, what are the most challenging issues to enable LTO? (Please select 2 issues)	☐ Conformance to new safety standard ☐ LTO Financing ☐ Identification of Ageing Degradation effects ☐ Equipment Aging Management ☐ Human Resources ☐ Update/evolution of Operational limits and conditions ☐ Access to Documentation ☐ Others (specify)
What is the order of magnitude of the investment needed to secure extension of the operating license (long-term operation of the installation)?	☐ [1 – 10M€] ☐ [10 – 50M€] ☐ [50 – 100M€] ☐ [>100M€]

Safety Regulation and Main Safety Issues

Is there a specific national regulation for Research Reactors?	☐ Yes ☐ No
What are for you the 3 main safety issues on which you will focus in the	☐ Ageing management ☐ Decommissioning Planning

near future? (Please select 3 issues)	☐ Emergency Preparedness ☐ Extended Shutdown ☐ Financial Resources ☐ Human Resources ☐ Human Factors ☐ Quality Assurance ☐ Radiation Protection ☐ Regulatory Supervision ☐ Safety Assessment ☐ Safety Culture ☐ Other (specify):

Periodic Safety Review (SR)

At which frequency do you perform Periodic Safety Review?	Every __ years
When was the last safety review analysis?	(Year)
Which were the topics that gathered the highest number of issues? (Please select less than 5 issues)	☐ Operating organization and reactor management; ☐ Safety committee(s); ☐ Training and qualification; ☐ Safety analysis; ☐ Site evaluation and protection against external hazards; ☐ Operational limits and conditions; ☐ Management system for the operation phase; ☐ Conduct of operations; ☐ Maintenance, periodic testing and inspection, ☐ Ageing management activities; ☐ Major modifications; ☐ Utilization and experiments; ☐ Radiation protection; ☐ Radioactive waste management; ☐ Emergency planning; ☐ Decommissioning plan; ☐ Safety culture.
Has a dedicated post-Fukushima Safety Analysis been performed?	☐ Yes ☐ No ☐ No, but post-Fukushima assessment was part of last SR

Peer Review Systems

In the last 10 years, has your installation been subject to external peer reviews (IAEA Peer Review (OMARR, IRRIA, INSARR), European Safety Organization Peer Review, Collaboration between Operators...)	Please specify the different peer reviews realized 1. Year – Entity in charge 2. Year – Entity in charge 3. Year – Entity in charge 4. ...

A17. Magnetic Resonance Imaging

A.17.1. General Principle

Magnetic resonance imaging (MRI) makes use of the magnetic properties of certain atomic nuclei. An example is the hydrogen nucleus (a single proton) present in water molecules, and therefore in all body tissues. The hydrogen nuclei behave like compass needles that are partially aligned by a strong magnetic field in the scanner. The nuclei can be rotated using radio waves, and they subsequently oscillate in the magnetic field while returning to equilibrium. Simultaneously they emit a radio signal. This is detected using antennas (coils) and can be used for making detailed images of body tissues.

Unlike some other medical imaging techniques, MRI does not involve radioactivity or ionising radiation. The frequencies used (typically 40-130 MHz) are in the normal radiofrequency range, and there are no adverse health effects. Very detailed images can be made of soft tissues such as muscle and brain.

The MR signal is sensitive to a broad range of influences, such as nuclear mobility, molecular structure, flow and diffusion. MRI is consequently a very flexible technique that provides measures of both structure and function (Diffusion weighted MRI).

A.17.2. MRI Situation in the EU

Technology improvements and cost equipment reduction permitted a strong development of MRI on the period 2000-2010, while growth has been limited since 2011 (7% increase on the period 2011-2015). This recent development enables EU countries to use up-to-date MRI technology (*roughly 80% of MRI equipment under 10 years old*). The latest evaluation of the installed base of MRI in EU (performed by COCIR³⁷⁹) is given in the table hereafter.

	2008	2011	2013	2015
IB 1-5 years - units	3568	4287	4002	4081
IB 6-10 years - units	2082	2546	2898	2947
IB >10 years - units	808	1178	1653	1587
	6458	8011	8553	8615

Figure 139: MRI installed Base in Nb of equipments for EU-28
Source COCIR

An average of 17 MRI equipment per Mhab was reached in 2015 on the EU scale, however large discrepancies exist between EU countries in terms of MRI installed capacity (from 3 to 30 MRI equipment per Million Habitant) and use (2 exams per day in average in Cyprus per equipment, against 45 per day in Hungary or 35 in France based on an assumption of a 5-days/wk use). Next figure illustrates the European large disparity in terms of MRI installed capacity.

³⁷⁹ European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry – Medical Imaging Equipment Age Profile & Density Edition 2016.

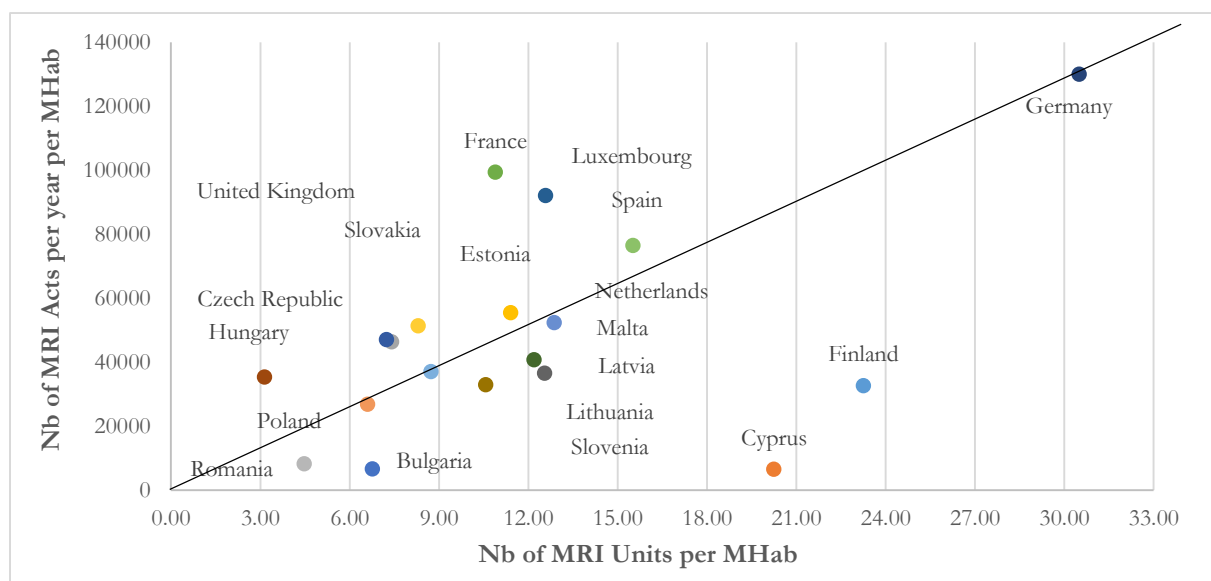


Figure 140 : MRI equipment in some EU-28 MS in 2014

Approximately 80 million MRI scans are conducted worldwide with 24 000 MRI scanners each year. European Union represents roughly one third of the MRI market.

A.17.3. MRI future evolutions

The quality and resolution of MRI have improved in the past two decades, primarily due to more powerful magnets. Electronics and imaging software have also improved as in other imaging technologies. At present, there is little that can be done to further improve the operation of the basic MRI system while significant limitations and challenges remain. Operating costs, installation complexity, and security concerns need to be addressed. Scan time—arguably the most important factor in operating costs and patient concerns—has not improved in any meaningful way.

Healthcare professionals are in agreement that shortening scan times while preserving image quality is the biggest game-changer. Future advances in MRI will focus more on simplifying imaging protocols so that data can be gathered faster and patients be screened more quickly.

A.17.4. Gadolinium contrast agent risks

Gadolinium contrast agents are used as contrast enhancers to improve image quality with magnetic resonance scans. Once injected, gadolinium interacts with the water molecules. As a result of this interaction, the water molecules give a stronger signal, helping to obtain a brighter image. Recent studies found that gadolinium deposition occurs in brain tissues following use of linear³⁸⁰ gadolinium contrast agents.

On July 21, 2017, the European Medicines Agency (EMA) confirmed previous recommendations to suspend the use of three linear gadolinium-based contrast agents³⁸¹ (GBCAs) used for MRIs, citing potential risks from brain deposition of gadolinium. The use of one other linear GBCA will be restricted to liver scans.

³⁸⁰ As compared to macrocyclic gadolinium agents, which are more stable and have a lower propensity to release gadolinium than linear agents

³⁸¹ http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500231824.pdf

Unequivocal data regarding the effects of multiple GBCA exposure are limited³⁸². However, the information regarding the thermodynamic stability constants for GBCAs, in vitro, animal, and human data, and the emerging data regarding gadolinium tissue accumulation in those with normal kidney function indicate that the potential toxicity associated with GBCA must be seriously and urgently considered.

This question must be addressed with retrospective and prospective cohort studies. Research providing additional mechanistic data is also paramount and will provide valuable information regarding how to prevent GBCA-related toxicity, treat existing GBCA-related health issues, guide the use of existing GBCAs, and direct the design of safer MRI contrast agents. The toxicity of gadolinium deposition in tissues shall be investigated, good practices have to be prepared in the EU to minimize injections to patients.

A.17.5. Diffusion MRI potential utilization for Breast Cancer Detection

Breast cancer (BC) is a global health problem and one of the principal causes of female morbidity and mortality (as illustrated by next figure). Its distribution (incidence, prevalence) and the economic burden it imposes on national health services make it a major public health concern both in developed and developing countries. The fight against breast cancer starts with the implementation of an efficient screening programme³⁸³ to detect cancer emergence as early as possible.

Estimated number of incident cases, females, European Union (EU-28) (top 10 cancer sites) in 2012 Estimated number of deaths, females, European Union (EU-28) (top 10 cancer sites) in 2012

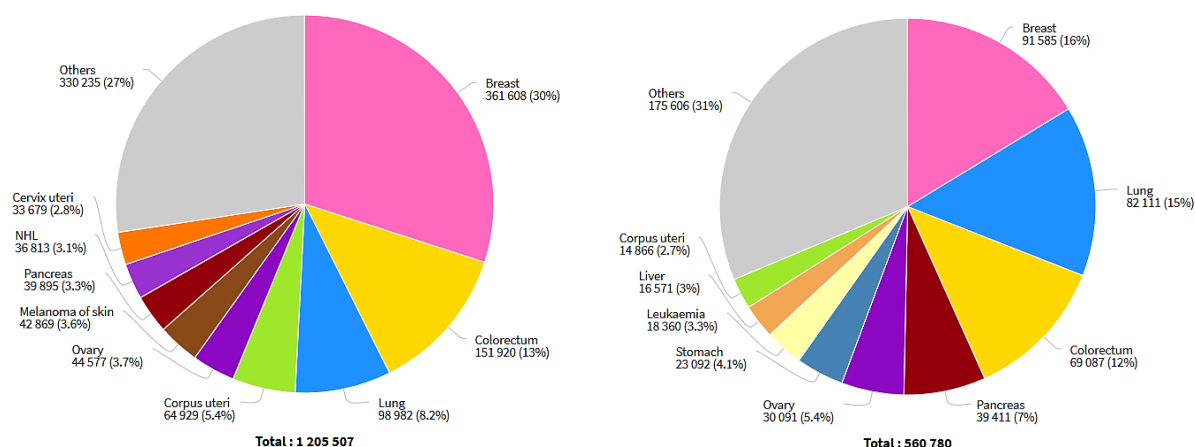


Figure 141: Estimated number of cancer incident cases and deaths – source gco.iarc.fr 2012

These screening programmes are mainly based on the utilization of X-Ray Mammograms, which lead to different issues: the regular delivery of radiation dose to organ at risk, and the relatively low detection efficiency of mammograms. The present capacity of MRI for detecting breast cancer (90.0%) appears significantly higher³⁸⁴ than that of mammography (37.5%) and ultrasound (37.5%). Despite this detection superiority, MRI use is today limited to certain patients “at risk”. A major disadvantage of MRI is that it

³⁸² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879157/>

³⁸³ A target rate screening participation objective of 75% has been defined by the EU, but large discrepancies where still existing in the EU in 2014 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4203333/#b76-ijo-45-05-1785>

³⁸⁴ <http://ascopubs.org/doi/full/10.1200/JCO.2014.56.8626>

gives more false positives, leading to unnecessary biopsies that counterbalance its direct benefit. However, the use of MRI Diffusion weighted imaging could solve this issue³⁸⁵ and make MRI a very promising alternative to X-Ray Mammograms. The cost of MRI examinations is also an obstacle for its development compared to Mammograms.

MRI development for breast cancer screening programme is linked to Diffusion Weighted Imaging development equipment cost optimization, with dedicated Breast MRI (mini) Machines. The development of such equipment could allow to dispose of a better alternative to Mammograms, without the use of radiation. A European funded cooperation project to assess such alternative could be beneficial to support MRI with diffusion weighted imaging.

³⁸⁵<http://www.sciencedirect.com/science/article/pii/S0378603X14001995>

A18. SNMMI Strategic Plan

The SNMMI³⁸⁶ Strategic Plan has the merit of listing exhaustively the impediments³⁸⁷ to NM development, all of which are gaps to be filled. Those deserving public support are highlighted in red.

SNMMI Strategic Plan (2017)³⁸⁸

Quality of Practice : Goal A: SNMMI members are known for high-quality, value-driven performance and delivery of patient-centered nuclear medicine practice.

1. (I) **Increase the development and dissemination of clinical guidance documents, including appropriate use criteria (AUC)**
 - a. Develop appropriate use criteria and procedure standards for NM/MI scans, therapies, and other procedures.
 - b. Collaborate with clinical decision support mechanism vendors to ensure proper implementation of AUC.
 - c. Review systematic review outsourcing and/or collaboration with other societies.
 - d. Ensure volunteer engagement to review AUC recommendations for clinical decision support.
 - e. Develop educational materials for AUC dissemination.
 - f. Develop and implement a communication plan to inform and educate members about AUCs.
 - g. Ensure appropriate staff resources.
2. (I) **Ensure the development of value/quality metrics for nuclear medicine.**
 - a. Identify existing appropriate quality measures (outcomes and processes) for nuclear medicine.
 - b. Develop new quality measures (if applicable) for nuclear medicine.
 - c. Explore collaborative clinical data registry development.
 - d. **Promote greater understanding of radiation benefits and levels in the general public and medical field.**
 - e. Develop relevant educational materials for members.
3. (I) **Standardize best practices to enhance operational efficiency.**
 - a. Streamline collaborative guideline development with other organizations (e.g., EANM).
 - b. Standardize the format for development and dissemination of procedure standards.
 - c. Develop templates for structured patient reports.
 - d. Explore SNMMI accreditation of nuclear medicine and therapy centers.
4. (I) **Expand continuing education options for practitioners.**
 - a. Work with existing programs to improve and expand NM/MI education.
5. (M) **Facilitate new service lines in nuclear medicine clinical settings.**
 - a. Identify novel ways to increase volume of NM/MI scans, therapies, and other procedures.
 - b. Educate nuclear medicine physicians and other colleagues.
 - c. Develop roadmaps for the nuclear medicine clinic of the future.
6. (L) **Improve recognition of the value of nuclear medicine with radiology practice.**
 - a. Forge alliances with radiology community to encourage greater understanding of NM/MI and obtain infrastructural support for NM/MI training and practice

Research and Discovery. Goal B: SNMMI has advanced the development and approval of nuclear medicine and molecular imaging technologies.

1. (I) **Encourage and promote research in the field.**
 - a. **Increase the number of facilitated collaborative research efforts among academic sites with industry**
 - b. Work with the Small Business Advisory Alliance³⁸⁹ to assist with clinical trials.

³⁸⁶ Society for Nuclear Medicine and Molecular Imaging (USA)

³⁸⁷ EANM has the same kind of analyses, but examining more in detail the US situation is particularly useful, given the fact that the USA are at the forefront in terms of Nuclear Medicine procedures.

³⁸⁸ Priority Keys are used for each action :

(I) = Immediate: work on this objective must be undertaken in the next fiscal year.

(M) = Mid-term: work on this objective should be undertaken in the next fiscal year if at all possible.

(L) = Later: work on this objective can wait until a subsequent fiscal year if necessary.

- c. Identify non-proprietary tracers that academic sites can help move to approval.
- d. Continue new business development within the LLC³⁹⁰.
- e. Reach out to experts in the field to involve them in work groups or coalitions that are producing new studies and papers.
- f. Support and foster collaboration between academia and industry; academia looks to industry to translate initial discoveries in patient care into new technology.
- g. Create networks to educate researchers so that studies are designed to produce results that the medical community needs and that address patient outcomes.
- h. Create and fund new research awards and grants.
- 2. (M+) Increase the number of initiatives targeting the discovery and validation of diagnostic radiopharmaceuticals, radiotherapeutics and instrumentation.
 - a. Organize meetings/events to involve experts from the field in identifying high-impact, unmet clinical needs.
- 3. (M) Improve the quality of nuclear medicine studies and literature.
 - a. Enhance the checklist for JNM³⁹¹ submission; enhance editorial enforcement.
 - b. Offer categorical session on study design.
 - c. Develop a series of papers to publish in JNM focusing on study design and the appropriate areas to include in papers submitted to JNM.
 - d. Create a central storage location for all resources.
- 4. (M) Increase funding for research awards.
 - a. Work with the Development Department to identify research funding opportunities.
 - b. Work with disease-specific organizations to identify potential areas of collaboration and research support.
- 5. (L) Enhance research on how nuclear medicine data can be implemented clinically in conjunction with informatics, etc.

Domain: **Workforce Pipeline and Life-Long Learning. Goal C: There is an appropriate number of qualified professionals working in the field of nuclear medicine.**

- 1. (I) Increase the supply of physicians qualified to practice nuclear medicine.
 - a. Increase collaboration with stakeholder organizations in nuclear medicine and radiology to develop training program pathways that provide high-quality graduate medical education leading to dual certification in nuclear medicine and radiology.
 - b. Advocate for development of institutional, ACGME³⁹², and federal policies that facilitate dual diagnostic radiology/nuclear medicine training.
 - c. Participate in activities (including AUR³⁹³, RSNA, ARRS, Aunt Minnie) to increase the visibility of nuclear medicine and encourage residents in diagnostic radiology to consider fellowship training in nuclear medicine.
 - d. Provide high-quality continuing education for nuclear medicine practitioners.
 - e. Provide a range of educational opportunities to help nuclear medicine physicians and radiologists develop practice competency and expertise in state-of-the-art nuclear medicine, molecular imaging, and radionuclide therapy.
 - f. Identify and conduct outreach to facilities, hospitals, and academic centers to ensure appropriate training and residency programs are implemented and supported.
 - g. Forge alliances with the American Board of Medical Specialties and radiology program directors to explain and demonstrate why NM/MI programs and expanded hours are important and

³⁸⁹ The Small Business Advisory Alliance (SBAA) offers the opportunity for companies to work in partnership with the SNMMI to build the future of nuclear medicine and molecular imaging through the SNMMI Value Initiative, demonstrating the crucial role of NM/MI in providing tailored, precise, valuable diagnostic and therapeutic care to patients.

³⁹⁰ In September 2008, the Society of Nuclear Medicine and Molecular Imaging created the Nuclear Medicine Clinical Trial Group, LLC to assist sponsors in effectively incorporating molecular imaging agents in multicenter trials. NMCTG aims to ensure that high-quality imaging is conducted to support drug or diagnostic clinical studies by offering a variety of proven tools developed by the Clinical Trials Network.

³⁹¹ Journal of Nuclear medicine

³⁹² Accreditation Council for Graduate Medical Education

³⁹³ AUR : Association of University Radiologists, RSNA : Radiological Society of North America, ARRS : American Roentgen Ray Society. AuntMinnie.com provides the first comprehensive community Internet site for radiologists and related professionals in the medical imaging industry.

necessary.

h. Increase the awareness of NM/MI in medical schools: create resources, provide information about the value of NM/MI professions—that the field is important, viable, exciting, and new.

i. Fund research grants to attract new talent into the field.

2. (I/M) Increase the supply of qualified nuclear medicine scientists.

a. Identify available training pathways for nuclear pharmacists and encourage development of new training programs.

b. Advocate for increased research funding, such as training grants, to support post-doctoral fellows preparing for careers in nuclear medicine research.

c. Identify and encourage sources of funding that can help to support medical physics residencies.

3. (M) Increase recognition of SNMMI as the professional home of all nuclear medicine professionals.

a. Ensure that educational programs provide value to current and potential members.

b. Use innovative and novel methods for providing educational content to members and non-members.

c. Support professional development and member engagement in the society.

4. (M/L) Increase awareness of NM/MI as an appealing and rewarding field for students interested in STEM careers (all professions—physicians, technologists, scientists).

a. Increase general outreach efforts to high schools and undergraduate colleges, coordinated with outreach activities.

b. Conduct focused outreach to undergraduate students training in physics and pharmacy

c. Conduct focused outreach to medical students and to first-year residents in diagnostic radiology to encourage training in nuclear medicine.

5. (L) Increase recognition of nuclear medicine technologists as the technologist experts in performing nuclear medicine imaging and therapy.

a. Support efforts of SNMMI Technologist Section to standardize nuclear medicine technologist training.

Domain: **Advocacy. Goal D: Policymakers understand the contribution of the nuclear medicine and molecular imaging field to improving patient outcomes.**

1. (I) Seek improvements in the integrity of the radioisotope supply chain and components.

2. (I) Improve understanding among those developing new radiotracers and radiotherapeutics of what type of evidence is needed by the FDA to approve them as “safe and effective” and by CMS³⁹⁴ to determine that they are “reasonable and necessary.”

a. Advocate for regulatory approval of emerging agents that are safe and effective.

b. Consistently advocate in legislative and regulatory venues about work that’s being done in the field to foster greater understanding and support of NM/MI work.

3. (I) Ensure adequate and appropriate reimbursement for NM/MI procedures.

a. Work with other societies and agencies (including insurance) to optimize reimbursement of current and future agents.

4. (I) Enhance state-level advocacy.

5. (L) Address U.S. pharmacopeia compounding issues.

6. (M) Increase visibility with federal legislators (i.e., sponsor an event, education programs, and/or an awards ceremony to raise awareness and recognize the work of those supporting pro-NM/MI legislation).

Domain: **Outreach**

Goal E: Patients and the medical community recognize the value of nuclear medicine, molecular imaging and radionuclide therapy.

1. (I) Increase the number of patients advocating in support of the value of radiopharmaceuticals.

a. Advertise patient advocacy activities on DiscoverMI³⁹⁵, Facebook, and Twitter.

b. Recruit local patient advocate champions for nuclear medicine.

c. Create fact sheets for patients with guidelines they should follow for all procedures.

d. Create “what to expect” videos.

2. (I) Increase referring physicians’ awareness of new radiopharmaceuticals.

³⁹⁴ Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) are part of the US Department of Health and Human Services

³⁹⁵ SNMMI’s patient website

- a. Focus on educating providers and patients outside SNMMI about available tests, ongoing research, and the best criteria and uses for available diagnostics.
- b. Recruit local MD³⁹⁶ champions.
- c. Create key slides on data supporting nuclear medicine procedures.
- d. Create physician fact sheets on new AUC topics
- e. Increase the number of referring physicians participating in SNMMI chapter programs.
- f. Develop CME³⁹⁷ roadshows for new radiopharmaceuticals and new AUCs.
- 3. (M) Improve collaboration with other medical societies.
 - a. Create new opportunities for joint (reciprocal) symposia.
 - b. Increase referring physician participation in SNMMI councils/centers.
 - c. Develop joint guidelines, white papers and review articles with ASNC³⁹⁸, ASCO, ASTRO, AUA, ATA, ASH, etc.
- 4. (M) Increase SNMMI's outreach efforts and resources within the imaging community.
 - a. Offer presentations at chapter meetings, at the Annual and Mid-Winter meetings, and via webinars.
 - b. Disseminate information about current initiatives to smaller NM/MI chapters to reach those who don't attend the Annual Meeting.
 - c. Offer a "Best of SNMMI" annual presentation at meetings of other imaging societies (RSNA, ARRS, ACR³⁹⁹, WMIS).
 - d. Host online journal clubs.
 - e. Reach radiology and medical school residency programs.
- 5. (M) Increase outreach to hospital administrators.
 - a. Collaborate with the Coding and Reimbursement Committee.
 - b. Present at the Radiology Business Management Association programs.
 - c. Collect data on relative value units and cost effectiveness for nuclear medicine procedures and implications for purchasing expensive technology.
- 6. (M) Expand financial resources dedicated to outreach activities.
 - a. Create proposal for industry funding.
 - b. Connect with industry to raise awareness about why they should support what's being done in the field.
 - c. Secure foundation funding.
 - d. Develop metrics of program success.
 - e. Ensure a 10% increase in funding each year.
 - f. Encourage philanthropy through patient advocacy.

³⁹⁶ Medical doctors

³⁹⁷ Continuing Medical Education

³⁹⁸ ASNC : American Society of Nuclear Cardiology, ASCO : American Society of Clinical Oncology, ASTRO: American Society for Radiation Oncology, AUA : American Urological Association, ATA : American Telemedicine Association, ASH : American Society of Haematology

³⁹⁹ ACR : American College of Radiology, WMIS : World Medical Imaging Congress

A19. *Intentionally blank*

A20. ESR 2014 Action Plan

In this 2014 plan, ESR calls on the EU institutions to:

QUALITY & SAFETY

- support the establishment of European quality and safety indicators for imaging
- support an audit of imaging equipment, doses, image quality and procedures of the medical imaging chain in Europe and to develop plans to modernise equipment⁴⁰⁰
- support efforts to improve communication with patients
- improve inter-institutional cooperation for more coherent action in the area of health
- support the EuroSafe Imaging campaign (www.eurosafeimaging.org) to raise awareness of the importance of radiation protection

EDUCATION & TRAINING

The ESR promotes intra-EU mobility of professionals in the context of the Europe 2020 strategy. For the radiology profession, it is essential that quality of care and patient safety are adequately secured in cross-border employment situations. Hence, The ESR calls on the EU institutions to:

- support the harmonisation of radiology training by endorsing the European Training Curriculum and the ESR European Diploma in Radiology
- support mandatory continuous medical education and continuous professional development for medical professionals throughout the EU
- support harmonisation in training for medical physicists and RTTs.

RESEARCH

Personalised medicine has led to a great heterogeneity of data and consequently a need for the integration of imaging and “omics”⁴⁰¹ data and the development of structured data repositories to facilitate personalised medicine and clinical trials. The ESR calls on the EU institutions to:

- recognise medical imaging as an integral part of personalised medicine
- support the standardisation and validation of imaging biomarkers
- support the development of European biobanks in medical imaging to improve interoperability and standardisation
- develop methods of integrating these data with “omics” databases

eHEALTH

Advances in information technology have revolutionised healthcare in general and radiology in particular and the current technological possibilities are paving the way for cross-border telemedicine services including teleradiology⁴⁰². Consequently, a need is arising for European standards. The ESR calls upon the EU institutions to:

- endorse the development of Clinical Decision Support systems to improve clinical workflow, appropriateness and training for referrers
- support the harmonisation of coding and terminology
- foster semantic interoperability

⁴⁰⁰ For instance, by setting new mandatory standards for renewed equipment

⁴⁰¹ refers to a field of study in biology ending in -omics, such as genomics, proteomics or metabolomics

⁴⁰² This is of particular interest in EU-28 MS suffering from a lack of radiologists, which seems an increasing trend in EU-28, as also observed for some specialties of radiotherapy (see chapter3.1)

- support the further development of picture archiving and communication systems (PACS) in order to ensure harmonised standards in data transmission and reporting
- revise the legal framework for teleradiology

A21. COCIR European Market

For getting the EU part of the global Ionizing radiation-based equipment market, COCIR data⁴⁰³ may be used as shown below:

Modality	EU-28 + Sw/Norge Market Value (including market coverage estimated rate) M€								Var 09 -16
	2009	2010	2011	2012	2013	2014	2015	2016	(%)
CT	593	578	506	491	454	402	489	462	-22,1
MRI	738	809	670	683	600	677	762	804	9,0
NM	249	245	200	200	200	158	196	214	-14,0
US	977	993	961	902	899	900	900	900	-7,9
X-Ray	1184	1288	1282	1120	1185	1191	1304	1145	-3,3
Total	3740	3913	3619	3396	3338	3328	3651	3525	-5,7
Total X-Ray	1776	1866	1788	1611	1639	1593	1793	1607	-9,6

Market values in red have been interpolated or assumed (no data for these years in the COCIR references)

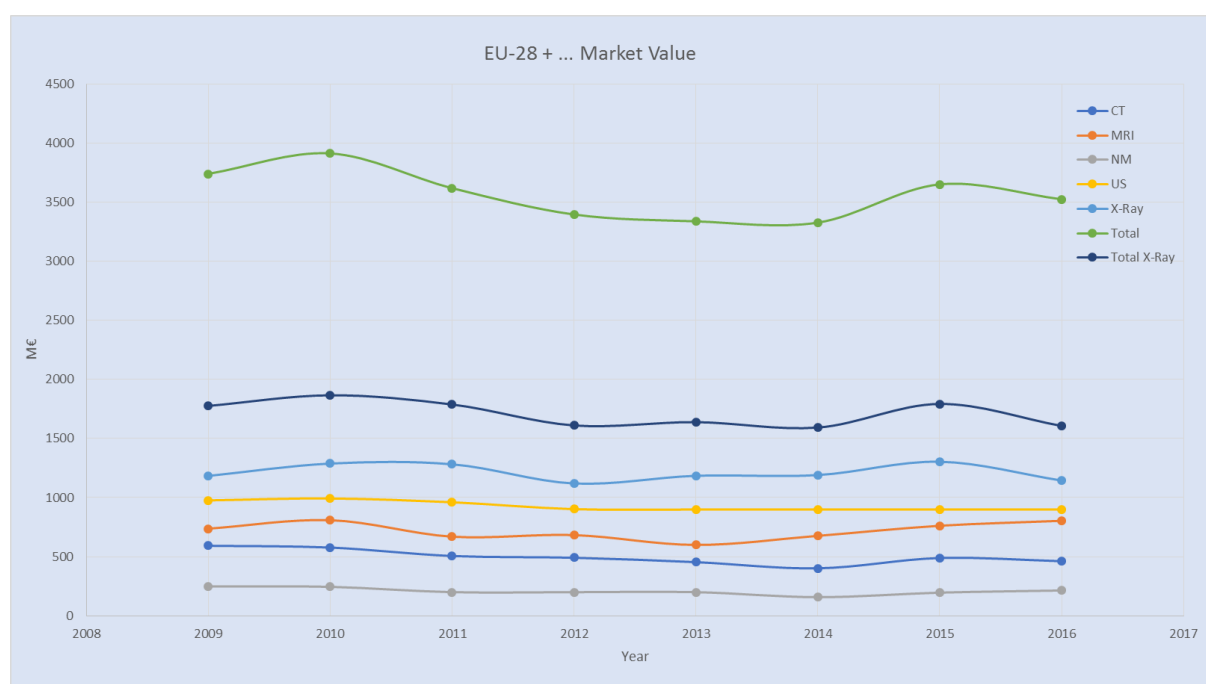


Table 55 : Imaging market Europe (COCIR SRI Status Reports data)

The table and figure above concern Estonia, Latvia, Lithuania, Bosnia, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, Slovenia, Ukraine, Portugal, Spain, Denmark, Finland, Norway, Sweden, Ireland, UK, Austria, Belgium, France, Germany, Greece, Italy, Netherlands and Switzerland.

The COCIR figures allow to estimate the European market of Ionizing radiation-based equipment (CT, NM, X-Ray) market to about 1,8 B€ (2016) and rather stable. It is unclear whether the Therapy part of the market is included, but in any case, it is a small part which does not change the conclusion below.

⁴⁰³ COCIR SELF-REGULATORY INITIATIVE FOR THE ECODSIGN OF MEDICAL IMAGING EQUIPMENT STATUS REPORTS 2010 to 2016 (see <http://www.cocir.org/initiatives/ecodesign-initiative/sri-status-reports.html>)

A22. The Xofigo® development story

The radiopharmaceutical Xofigo® (Bayer) development story: a private initiative /SME/Public/Financiers/Large Pharmaceutical company successful (and long) process

1. The first years. A startup, Algeta ASA, was founded in 1997 in Oslo, Norway, as a private biotechnology and pharmaceutical company under the name Anticancer Therapeutic Inventions AS by Roy Larsen, a nuclear chemist from the University of Oslo, and Øyvind Bruland, professor of oncology at Norwegian Radium Hospital, based on their research on alpha-emitting cancer therapeutics. The company's research and development focus lay in the field of alpha-particle emitting radiopharmaceuticals. The name was changed to Algeta in 2003.

During these years, Algeta developed at the laboratory scale, in collaboration with the Isotope Laboratory at the Institute for Energy Technology (IFE) from 2001, a radiopharmaceutical based on ^{223}Ra dichloride, they called Alpharadin, a radiotherapeutic drug which is supplied as injectable sterile solution. The active ingredient alpha particle emitting radioisotope radium-223 mimics calcium and forms complexes with hydroxyapatite at areas where increased bone turnover takes place, such as cancer bone metastasis. Radium-223 can be produced efficiently in large amounts. In 2006, Bruland explained the production process: sources of precursor ^{227}Ac ($t_{1/2} = 21.7$ years) can be used as a long-term operating generator for ^{223}Ra . Actinium-227 is produced by neutron irradiation of natural Ra-226 . Moreover, the half-life of ^{223}Ra provides sufficient time for its preparation, distribution (including long distance shipment), and administration to patients. Its low γ -irradiation is favourable from the point of view of handling, radiation protection, and treatment on an outpatient basis. Radium-223 produced from $^{227}\text{Ac}/^{227}\text{Th}$ is purified using Ac-resin to immobilize ^{227}Ac and ^{227}Th . According to procedures used by Algeta ASA, the Alpharadin product concentrate (dissolved $^{223}\text{RaCl}_2$) is tested for radionuclide purity by γ -spectroscopy. The concentrate of ^{223}Ra in NaCl and Na citrate is transferred to a good manufacturing practices (GMP) radiopharmacy unit, the Isotope Laboratory at Institute for Energy Technology (Kjeller, Norway), where the sterile production is done. Isotonicity, pH, and activity concentration are adjusted. Product is dispensed into vials, and the vials are autoclaved whereas a sample is kept aside for pathogen and pyrogen testing. The final product is shipped in sterile vials capped with a sealed rubber membrane penetrable to syringes. With Alpharadin seeming really promising, Algeta decided to pursue the development (e.g. clinical trials). Additional financing became necessary.

2. Early fund raising and Public offering: Algeta raised its financing round in 2005 with a total amount of €23 million. The financing round was led by new investors HealthCap, Advent Venture and SR One. In March 2007, the company went public and traded in the Oslo Stock Exchange under the ticker symbol ALGETA and raised \$41 million.

3. Development: Algeta Bayer deals. In September 2009, Algeta and Bayer AG anchored a development and commercialization deal for Xofigo® (new name of Alpharadin) with the total deal size of \$800 million. The company received the first \$61 million up front through a deal with Bayer for the global development and commercialization of Alpharadin.

Algeta had an option to co-promote in the U.S. under a 50% profit-share arrangement. Bayer would commercialize Alpharadin globally and pay tiered double-digit royalties on net sales in markets where there is no co-promotion. Bayer would contribute a majority of the future development costs of Alpharadin as a treatment for bone metastases. It would also fully fund any additional late-stage trials. Algeta could

receive up to \$800 million through the deal, including the \$61 million up-front payment, plus development, production, and commercialization milestones. In January 2010, Algeta signed a contract with the Institute for Energy Technology (IFE) for Commercial Manufacturing of Xofigo/Alpharadin: "The Institute for Energy Technology (IFE) is collaborating with Algeta on the clinical- and commercial-scale manufacture and supply of the latter's Phase III compound, Alpharadin (radium-223 chloride). The IFE has been Algeta's manufacturer and supply partner for Alpharadin for all clinical trials to date. Alpharadin, administered as an injection, is currently undergoing an international Phase III trial in patients with hormone-refractory prostate cancer (HRPC) and skeletal metastases. In December the first clinical centre for the trial in the U.S. started enrolling patients. An estimated 8 million Euros (75 mill NOK) over 2-3 years will be invested into the new production plant, scheduled to be ready in 2012/2013".

3. Xofigo® : The product received U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in May 2013 and November 2013, respectively, to treat castration-resistant prostate cancer, symptomatic bone metastases and unknown visceral metastatic disease. Xofigo® became quickly the first marketed alpha-particle emitting radiopharmaceutical for cancer treatment (TAT).

4. Industrialization : In December 2013, Bayer offered a full acquisition of Algeta. The largest shareholder HealthCap pre-approved the deal which was completed in March 2014 for €1.97 billion⁴⁰⁴.

⁴⁰⁴ Bayer Annual report 2015

A23. Food irradiation situation in the EU

Irradiation is one of the few food technologies that can maintain food quality and address food safety and security problems without significantly affecting a food's sensory or nutritional attributes. Irradiation has the ability to slow ripening, inhibit sprouting in bulbs and tubers, control spoilage and foodborne pathogenic microorganisms as well as prevent the spread of invasive insect pests (as a quarantine treatment for fresh produce, making any associated insects incapable of reproducing and therefore unable to colonize new territory). The process does not raise food temperatures, leaves no harmful residues and can be applied to packaged food, thus limiting the chances of re-infestation or re-contamination.

Situation in the EU

Currently, the foods & food ingredients authorised for irradiation in the EU are

- Fruit and vegetables including root vegetables
- Cereals, cereal flakes, rice flour
- Spices, condiments
- Fish, shellfish
- Fresh meats, poultry, frog legs
- Raw milk camembert
- Gum arabic, casein/caseinates, egg white
- Blood products

Regulations applicable in Europe are Directives 1999/2 & 3/EC and applicable national laws are depicted in the table below:

List of Member States' authorisations of food and food ingredients which may be treated with ionising radiation

(According to Article 4(6) of Directive 1999/2/EC of the European Parliament and of the Council on the approximation of the laws of the Member States concerning foods and food ingredients treated with ionising radiation)

(2009/C 283/02)

(This text cancels and replaces the text published in Official Journal C 112 of 12 May 2006, p. 6)

Product	Authorized at the given maximum overall average absorbed radiation dose (kGy)						
	BE	CZ	FR	IT	NL	PL	UK
Deep frozen aromatic herbs	10	10	10				
Potatoes	0,15	0,2		0,15		0,1	0,2
Yams		0,2					0,2
Onions	0,15	0,2	0,075	0,15		0,06	0,2
Garlic	0,15	0,2	0,075	0,15		0,15	0,2
Shallots	0,15	0,2	0,075				0,2
Vegetables, incl. pulses	1	1					1
Pulses		1			1		
Fruit (incl. fungi, tomato, rhubarb)	2	2					2
Strawberries	2	2					
Dried vegetables and fruits	1	1	1		1		
Cereals	1	1					1
Dried fruit		1					
Flakes and germs of cereals for milk products	10	10	10				
Flakes from cereals		1			1		
Rice flour	4	4	4				
Gum arabic	3	3	3		3		
Chicken meat		7			7		
Poultry	5	5	5				
Poultry (domestic fowls, geese, ducks, guinea fowls, pigeons, quails, and turkeys)	7	7					7
Mechanically recovered poultry meat	5	5	5				
Offal of poultry	5	5	5				
Frozen frog legs	5	5	5		5		
Dehydrated blood, plasma, coagulates	10	10	10				
Fish and shellfish (incl. eels, crustaceans and molluscs)	3	3					3
Frozen peeled or decapitated shrimps	5	5	5				
Shrimps					3		
Egg white	3	3	3		3		
Casein, caseinates	6	6	6				

There is not yet convergence among the EU-28 MS on the list of authorized foods and irradiation levels.

A24. Advisory Panel written comments

A.24.1. Position paper from European Society of Radiology

European Society of Radiology Input to SAMIRA Project February 2018

The [European Society of Radiology \(ESR\)](#) is pleased to be a member of the Advisory Board of the SAMIRA project and welcomes the opportunity to contribute to the development of a strategic agenda for medical, industrial and research applications of nuclear and radiation technology.

The ESR considers it important to include in the final SAMIRA report some concrete recommendations addressed to European policy makers.

From the radiology perspective, there is a need to address the following challenges at strategic level:

a. Moving from a regulatory approach to the integration of radiation protection concepts with health policies

- The current disconnection between radiation protection bodies and health policy bodies needs to be addressed.
- As regards education, Europe lacks a structured radiation protection programme. Radiation protection should become a clinical science and established as an integral part of medical training curricula.
- A radiation protection concept based on good practice should be integrated into a broader concept for good practice in healthcare.
- In many European countries, budget cuts in healthcare are at the expense of quality of care and patient safety. The concept of quality and safety and related cost need to become an integral part of national healthcare plans.
- The importance of updating medical imaging equipment needs to be promoted with the funders of healthcare, as regulators' buy-in alone does not suffice. European financial support to be considered to enable Member States to update their equipment base.

b. Promoting a European imaging database

- Europe lacks reliable data on the number of imaging procedures performed and related dose data. It is thus important to advocate the mandatory use of automatic dose collection systems.
- The potential of big data should be leveraged for medical imaging. Further epidemiological studies are needed to explore the health impact of low dose exposure to ionising radiation. The [MEDIRAD](#) project is one contribution in that direction, but certainly more research and related funding are needed.
- Personal medicine has been promoted and been seen as a paradigm change in healthcare in many countries in Europe. However, related programmes do not consider imaging data. There is an urgent need to fully

embrace medical imaging within personalised medicine concepts.

- As regards research in medical radiation protection, outreach to and alignment with the European platforms [MELODI](#) and [EURAMED](#) are recommended, in particular as regards their strategic research agendas.

c. Addressing the heterogeneity of imaging use and practice in EU 28

- Statistics on availability and use of imaging equipment show a significant heterogeneity across EU member states.
- There is an urgent need to develop key indicators for quality and safety in medical imaging across Europe.
- Heterogeneity also prevails in medical imaging education and training. The development of European training curricula for medical specialties and European diplomas should be encouraged to remedy the situation. Good practice examples are available from the [ESR](#).

d. Addressing the need for a better integration of radiology and nuclear medicine

- Collaboration between the two specialties should be encouraged and an integrated approach pursued in the interest of quality and safety. Political roadblocks are to be eliminated and incentives need to be created for an integrated, collaborative approach. The successful integration of medical imaging and nuclear medicine in the Netherlands can be taken as a good practice example.

e. Improving the public perception of imaging

- Dialogue with patient associations should be fostered.
- Paediatric imaging should be a focus area.
- Consider separating medical imaging from the nuclear sector authorities or reconsider wording to sound less frightening to patients and the public when dealing with medical applications using ionising radiation (“nuclear”, “safety & security” etc. may sound threatening to the public).

A.24.2. APAE comments

APAE Coordinator Dr. Angeles FAUS-GOLFE – Advisory Panel Member

Dr.Faus-Golfe confirmed that, a priori, subject to further consideration, the priorities for possible EU interventions could be put

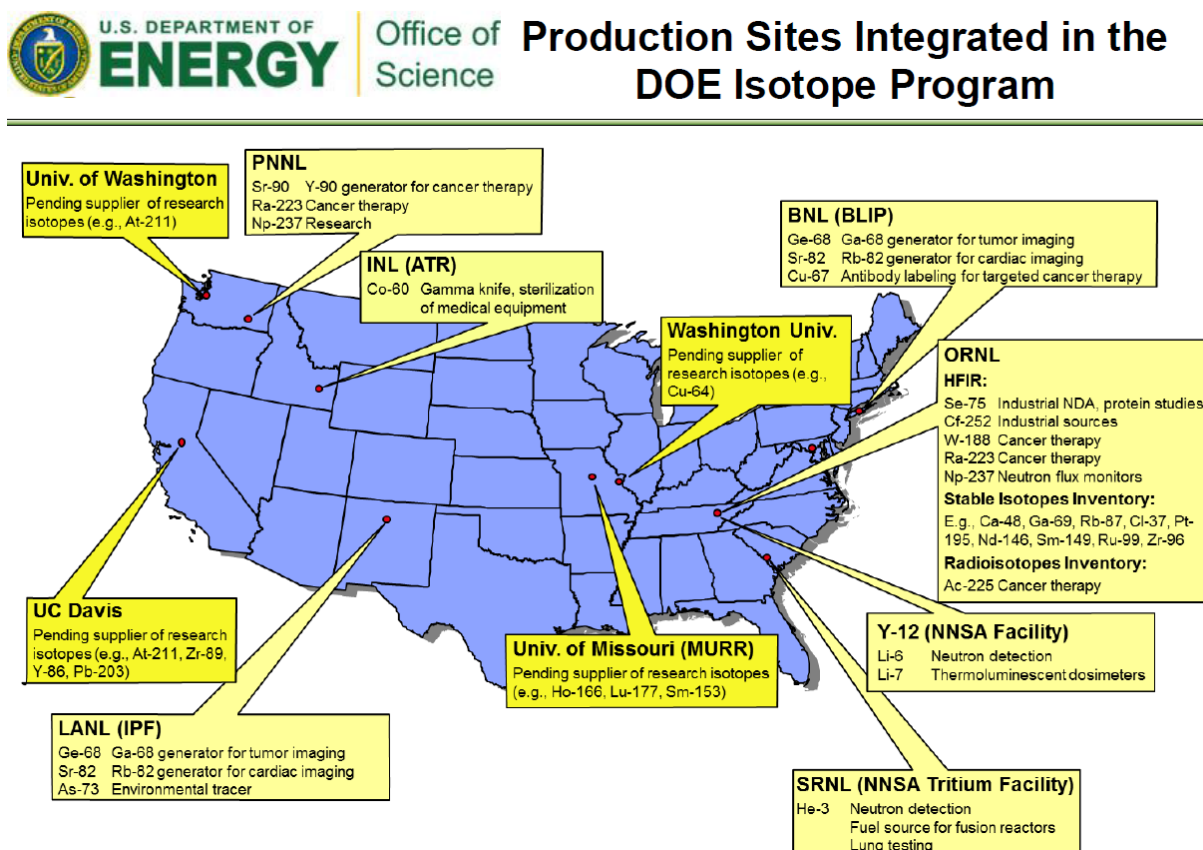
- 1) on the regulations aspects of the APAE recommendations expressed in the EUCARD2 final report
- 2) on the education and training aspects of these recommendations
- 3) on the need for a socio-political environment more conducive to non-energy ionizing radiation applications and research

A25. Isotopes development in the USA⁴⁰⁵

The mission of the DOE Isotope Program is threefold:

- Produce and/or distribute radioactive and stable priority isotopes that are in short supply, associated by-products, surplus materials and related isotope services. Priority isotopes are defined as those that are not produced domestically in sufficient quantity or quality to meet the needs of research and applications important to the Nation.
- Maintain the infrastructure required to produce and supply isotope products and related services.
- Conduct R&D on new and improved isotope production and processing techniques which can make available new isotopes for research and applications.

The priority isotopes and the production sites integrated in the DOE isotopes program are depicted hereafter.



The working programme set up by the USA :

⁴⁰⁵ DOE Isotope Program. 8th International Conference on Isotopes August 25, 2014. Marc Garland (DOE)

- Maintain a continuous dialogue with all interested federal agencies and commercial isotope customers to forecast and match realistic isotope demand and achievable production capabilities.
- Coordinate production capabilities and supporting research to facilitate networking among existing DOE, commercial, and academic facilities.
- Support a sustained research program in the base budget to enhance the capabilities of the isotope program in the production and supply of isotopes generated from reactors, accelerators, and separators.
- Devise processes for the isotope program to better communicate with users, researchers, customers, students, and the public and to seek advice from experts.
- Encourage the use of isotopes for research through reliable availability at affordable prices.
- Increase the robustness and agility of isotope transportation both nationally and internationally.
- Invest in workforce development in a multipronged approach, reaching out to students, post-doctoral fellows, and faculty through professional training, curriculum development, and meeting/workshop participation.
- Construct and operate an electromagnetic isotope separator facility for stable and long-lived radioactive isotopes.
- Construct and operate a variable-energy, high-current, multi-particle accelerator and supporting facilities that have the primary mission of isotope production.

And the isotopes under development are :

- Ac-225:Developing accelerator production capability
- At-211:Funding production development at four institutions to establish nationwide availability
- Am-241:Initiated project to produce Am-241 in association with an industrial consortium
- C-14: Investigating economic feasibility of reactor production
- Cd-109:Working with industry to assess product specific activity
- Co-57:Evaluating production of Co-57 for commercial source fabricators
- Cs-137 HSA: Pursuing reactor production feasibility for research applications
- Cu-64:Funding production development at multiple institutions
- Gd-153:Pursuing feasibility of reactor production
- Ho-166:Establishing reactor production capability
- I-124:Funding production development at one institution

- K-40:Evaluating possibility of reactor production by irradiating K rather than electromagnetically enriching K-40
- Li-7:Working to establish reserve for nuclear power industry to mitigate potential shortage
- Np-236: Pursuing feasibility of accelerator-based production for security reference materials
- Pa-231:Purifying 100 mg for applications such as fuel cycle research
- Sr-89: Investigating economic feasibility of reactor production
- U-233:Acquisition of mass separated U-233 for research applications
- U-234:Investigating alternatives for provision of U-234 for neutron flux monitors
- Zn-62/Cu-62:Funding production development for Zn-62 for use in a generator to provide the positron emitter Cu-62
- Zr-89:Funding production development at multiple institutions