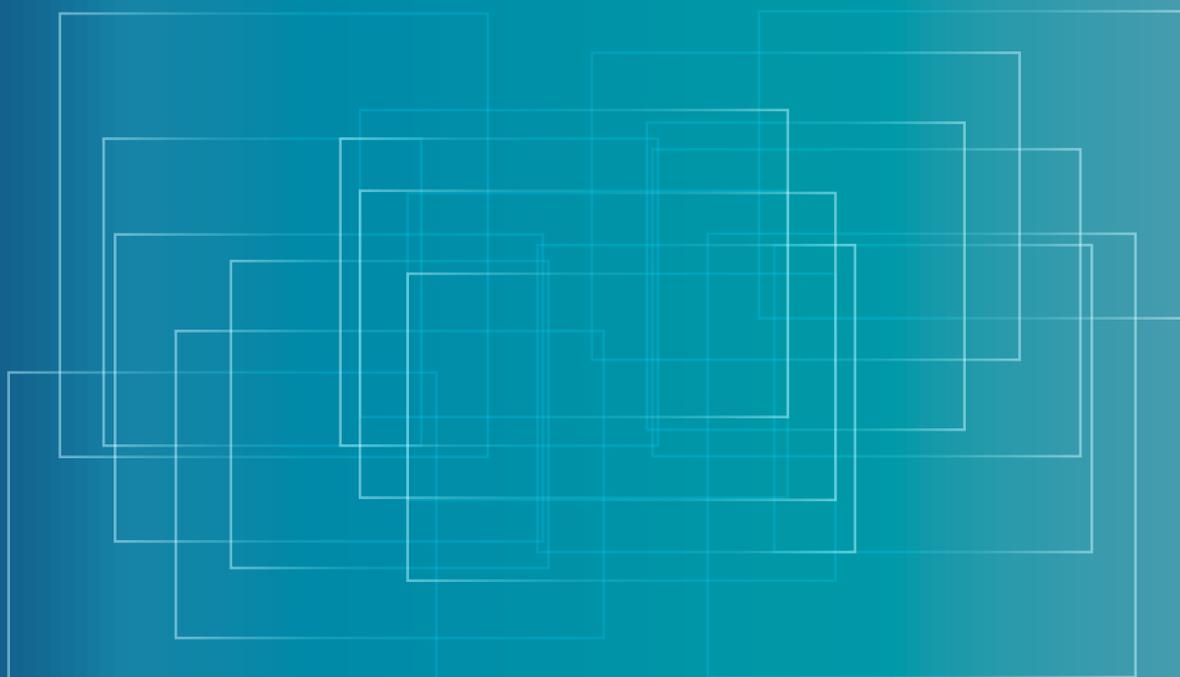


# Alternative Radionuclide Production with a Cyclotron



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ALTERNATIVE RADIONUCLIDE  
PRODUCTION  
WITH A CYCLOTRON

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## FOREWORD

Cyclotrons are currently used for the preparation of a wide variety of radionuclides that have applications in single photon emission computed tomography (SPECT) and positron emission tomography (PET). Consequently, there is high Member State demand for support in the area of radiopharmaceutical production using cyclotron produced radioisotopes. There are now more than 1300 cyclotron facilities worldwide, and that number is growing every year, with the highest rate of growth occurring in developing countries.

The IAEA has carried out several projects to support radionuclide production using cyclotrons. To help Member States build expertise in the field of medical isotope production, it was decided to produce a technical publication covering the production of alternative radionuclides (other than the well established PET radionuclides) with cyclotrons. The primary aim was to demonstrate the significant potential for the development of new radionuclides at existing facilities with low and medium energy cyclotrons and to help operators and decision makers in planning upgrades of or building new cyclotron facilities.

Work on this publication was initiated during a consultants' meeting held from 12 to 16 November 2018 at the IAEA Headquarters in Vienna, with contributions from dedicated experts in the fields of cyclotron utilization, radiochemical processing, isotope production and cyclotron based radiopharmaceutical preparation for clinical investigations. The publication is intended to provide information on practical production methods for cyclotron based radionuclides, with optimized purification techniques to obtain high specific activity and chemical purity for use in the medical-scale labelling of molecules.

This publication briefly describes the potential radionuclide production routes using cyclotrons in different energy ranges; methods for the development of targets; and the chemistry for the separation of radionuclides from target materials for the production of these radionuclides. The target readership of this publication includes scientists, operators interested in putting this technology into practice, technologists already working with cyclotrons who wish to enhance the utility of existing machines, and managers in the process of setting up radionuclide facilities in their countries. Students working towards higher level degrees in related fields may also benefit from this publication.

The IAEA wishes to thank all the participating consultants and contributors to this publication for their valuable input, and J.S. Vera Araujo for editorial support. The IAEA officer responsible for this publication was A. Jalilian of the Division of Physical and Chemical Sciences.

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# 1. INTRODUCTION

## 1.1. BACKGROUND

Radionuclides produced with cyclotrons and their corresponding radiopharmaceuticals have demonstrated their enormous value in basic medical research, disease diagnosis and radiotherapy treatment. There are more than 1300 cyclotron facilities worldwide, and that number is growing every year. Cyclotrons come with different energy ranges and associated equipment, such as target ports with or without beamlines, depending on the functions for which they are intended. Most of these cyclotrons are not running at full capacity and production is often limited to one or two positron emission tomography (PET) tracers that are in routine clinical use. Beam time in many cyclotron facilities is underutilized, with only about 15 to 20 hours per week being devoted to radionuclide production. If this time could be utilized to enable research and development (R&D) activities and to produce other radionuclides that have demonstrated or potential clinical applications, the nuclear medicine and research programmes of the Member States would clearly benefit. Depending on the energy and type of the accelerated particle, cyclotrons could be ideal for producing the standard PET and single photon emission computed tomography (SPECT) radioisotopes, but could also be well suited to the production of several non-standard positron or single photon emitting radionuclides. The development of such radionuclides involves the study and optimization of aspects such as nuclear data, proper and cost effective targetry, chemical processing, automation and quality control. In order to produce a viable product with high labelling efficiency, both the radionuclidic purity and the specific radioactivity of the product need to be maintained at a very high level.

The development of new radiopharmaceuticals that can be routinely used for diagnosis or for evaluation of radiotherapy would provide valuable additions to the arsenal available to nuclear medicine physicians. However, there are several other limiting factors in the production and use of new radiopharmaceuticals. The time necessary for conversion from radionuclide to radiopharmaceutical is significant and requires specialists to carry out the synthesis and quality control of these radiotracers. Many cyclotron facilities have been designed for the production of a single product and may require additional space in order to produce new radionuclides. More (and perhaps different) equipment may be necessary to carry out synthesis and product testing. There will be different radiation protection requirements and waste disposal considerations with new radionuclides. More personnel will be required, not only to perform synthesis and quality control, but also to keep production records and maintain compliance with good manufacturing practices. Radiation safety and regulatory issues regarding patients are a concern, since these radionuclides are typically longer lived and may not be excreted quickly. In order to design clinical trials for new radiopharmaceuticals, there must be a reliable supply of radionuclides and a reliable synthesis process for the radiopharmaceutical.

The field of the use of radionuclides for diagnostic imaging and therapy is still in the early stages of development, and possibilities for expanding the efficacy and value of radiotracers and radiopharmaceuticals are available. In diagnosis, tracers are needed that are very specific to a particular biological process, and using some of these alternative radionuclides may be the key to finding those tracers. For example, being able to accurately assess the turnover rate of enzymes could be particularly useful for some diseases. Some radiometals and even radioactive non-metals could be very useful for this purpose. In radiotherapy, agents are needed that will adhere only to diseased cells and not attach to healthy cells to enhance effectiveness and minimize peripheral damage. Achieving a high radiotherapeutic agent to target tissue ratio, especially with alpha emitters, holds great promise.

## 1.2. OBJECTIVE

This publication is intended to provide information on practical production routes and on the optimal separation and purification of alternative (non-traditional) cyclotron produced PET radionuclides, in order to achieve high specific radioactivity and chemical purity suitable for labelling molecules of medical interest and to make effective use of the spare capacity available in medical cyclotron centres.

Guidance provided here, describing good practices, represents expert opinion but does not constitute recommendations made on the basis of a consensus of Member States.

## 1.3. SCOPE

This publication describes the potential radionuclide production routes using cyclotrons in different energy ranges; methods for the development of targets; and the chemistry for the separation of radionuclides from target materials for production of these radionuclides. Traditional PET radionuclides such as  $^{18}\text{F}$ ,  $^{11}\text{C}$ ,  $^{15}\text{O}$  and  $^{13}\text{N}$  are omitted from this scope, as they are covered in detail elsewhere [1, 2].

This publication is compiled from the contributions of consultants who have vast experience in the area of radioisotope production and the preparation of cyclotron based radiopharmaceuticals for clinical applications. Consequently, this publication contains an overview of the production of potential radionuclides using cyclotron beams of proton, deuteron or alpha, techniques on the preparation of targets, irradiation of targets under high beam currents, target processing, target recovery, etc. This publication will be of interest to scientists, operators and decision makers wishing to select and install appropriate medical cyclotrons based on national and regional needs. Young scientists and graduate students looking at the R&D aspects of cyclotron based radioisotopes may also benefit from this publication.

## 1.4. STRUCTURE

Sections 2 and 3 provide basic cyclotron parameters, including cyclotron energy classification and an overview of the development of cyclotron targetry, including range and energy calculations, respectively. Section 4 provides information on the alternative radionuclides that can be produced efficiently on cyclotrons of different energies and gives guidance on the optimum energy range for the related nuclear reactions to avoid radioisotopic and radionuclidic impurities.

# 2. CYCLOTRON PARAMETERS

## 2.1. GENERAL CONSIDERATIONS

Converting the atoms of one element into those of another is a major achievement in radionuclide production. The method involves altering the number of protons and/or neutrons in the nucleus (target material). For instance, while a neutron is added without the emission of particles, the final nuclide possesses the same chemical properties as the target nuclide. However, if the target nucleus is bombarded with a charged particle, the resulting nucleus will be of a different element. Depending on several parameters, the exact types of nuclear reactions that a target undergoes are different. These parameters include the type of bombarding particle, the binding energy of the nucleus and the energy of the projectile.

A more complete description of the physics involved in radionuclide production with a cyclotron can be found in Ref. [3].

In 1936, one of the most useful models for nuclear reactions, the nucleus model, was introduced by Bohr. According to this model the energy of a charged particle is distributed throughout the compound nucleus followed by incident particle absorption into the nucleus of the target materials. At this stage, before decomposing with the emission of particles, the nucleus comes to some form of equilibrium. The two steps (i.e. production of a compound nuclide and emission) are independent. The evaporation of the particles is considered independent of the formation process, no matter how the compound nucleus arrived at the excitation level. The total amount of excitation energy contained in the nucleus is dependent on the relative masses of the nucleus and the incoming particle, the kinetic energy of the particle and the binding energy of the particle in the nucleus. The excited nucleus can decompose along several channels, with the probability of the nucleus decaying along a certain channel being directly proportional to the cross-section.

There is a minimum energy level below which a nuclear reaction will not occur except by tunnelling effects. When the compound nucleus decomposes, the kinetic energy of all the products may be either greater or less than the total kinetic energy of all the reactants. If the kinetic energy of the products is greater, the reaction is said to be exoergic. If the kinetic energy of the products is less than the reactants, the reaction is endoergic. The magnitude of this difference is called the  $Q$  value.<sup>1</sup> If the reaction is exoergic,  $Q$  values are positive; if the reaction is endoergic,  $Q$  values are negative. The threshold energy of a nuclear reaction is defined as the minimum projectile energy necessary to satisfy mass-energy and momentum conservation. The incident particle energy must be sufficient to overcome both the Coulomb barrier and a negative  $Q$  of the reaction. Particles with energies below this barrier have a very low probability of inducing a nuclear reaction. The Coulomb barrier is a measure of the nucleus–nucleus charge repulsion. It is directly related to the atomic number,  $Z$ , of both the particle and the target nucleus.

If the incoming projectile has an energy sufficient to overcome the Coulomb barrier and excite the nucleus, the resulting reaction will cause particles to be ejected from the target nucleus. By carefully selecting the target nucleus, the bombarding particle and its energy, it is possible to produce a specific radionuclide. Interestingly, despite the fact that Lawrence's cyclotron produced the first radionuclides in the 1930s, it took three more decades before cyclotron produced radionuclides began to play a major role in radiopharmaceutical production. The technology of cyclotrons has improved significantly over recent decades. Commercially available cyclotrons are now highly compact, rugged machines, are relatively easy to operate using computer controls and can reliably produce a variety of important radioisotopes, mostly for medical uses. One important advantage of cyclotron produced radionuclides is that it is possible to produce radionuclides with high specific activities through the  $(p,xn)$  and  $(p,\alpha)$  reactions since the product is a different element than the target. Another significant advantage is that less radioactive waste is generated from charged particle reactions compared with neutron reactions. A drawback of these charged particle reactions is that in some cases an enriched target material must be used to produce the required quantity of a radiopharmaceutical. Charged particle and neutron reactions are complementary to each other, since charged particle reactions typically lead to proton-rich radionuclides, and neutron-induced reactions typically lead to neutron-rich radionuclides. In some cases, depending on target material selection, a particular nuclide may be produced via both routes.

## 2.2. POSITIVE VERSUS NEGATIVE ION CYCLOTRONS

Cyclotrons can accelerate either positive or negative ions. The principal differences between the positive ion cyclotron and the negative ion cyclotron are the methods of extracting the beam and the corresponding vacuum requirements. The difference between the extraction techniques has implications in terms of the vacuum requirements and the uniformity of the internal and extracted beams. In the positive

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<sup>1</sup> For an example of a  $Q$  value calculator, see <https://www.nndc.bnl.gov>

ion cyclotron, the accelerated ions are positive ions ( $H^+$ ,  $D^+$ ,  ${}^3He^{+2}$  and  ${}^4He^{+2}$ ) and are extracted from the cyclotron by being pushed out of their orbits with an electrostatically charged bar called a deflector. The deflection of the particles is such that they are pushed into a new orbit that leads out of the cyclotron's acceleration chamber.

This method of extraction is due mainly to the fact that the ion sources tend to produce far more positive ions than negative ions. The disadvantage of this method is that the extraction efficiency is rather low (40–95%) compared with negative ion machines. In general, positive ion cyclotrons do not require as good a vacuum compared with negative ion cyclotrons. The use of a septum and deflector implies a greater amount of activation, which needs to be considered when maintenance of the cyclotron becomes necessary.

With the development of better ion sources that could produce larger quantities of negative ions, it became practical to accelerate negative ions ( $H^-$ ,  $D^-$ ). In this case the extraction is simpler and more efficient, since the negative ions could be converted to positive ions by passing the beam through a thin carbon foil. Once the negative ions are converted, the magnetic field sends them in the opposite direction and out of the cyclotron's acceleration chamber. The extraction efficiency using this method is close to 100%, which improves the beam current and reduces the activation inside the machine. The negative ion machines have a more uniform beam shape, higher extraction efficiency and less activation of the interior of the machine. As a result, negative ion systems have become the standard for proton and/or deuterium cyclotrons.

A high vacuum environment is required for optimum negative ion cyclotron performance. For the best maintenance and performance, the foils that strip the charge off the negatively charged hydrogen ion (strippers) need to be changed routinely. In all types of machines, the ion source filament also needs to be changed on a routine basis. Recently manufactured positive ion cyclotrons using a split septum require far less maintenance than the previous generations of cyclotrons using a notched septum. It is not possible to create negative helium ions in a negative ion cyclotron and therefore  ${}^3He$  and alpha ( ${}^4He$ ) particle beams are no longer available on most commercial cyclotrons today. However, the principal radionuclides used in medical applications can generally be produced by protons or deuterons, and thus the simplicity of the design has resulted in cyclotrons which accelerate  $H^-$  and  $D^-$  ions capable of two or more simultaneous beams of varying energies and intensities. Having an alpha beam opens the possibility of producing some radionuclides, such as  ${}^{211}At$ , that cannot be produced in any other way. For this reason, positive ion cyclotrons still have a place in cyclotron technology.

## 2.3. CYCLOTRON FACILITIES

The types of cyclotrons fit into several categories. In general, cyclotrons are categorized by energy range. Most of the cyclotrons currently in use are in the first two categories (i.e. <12 MeV and 12–20 MeV). As mentioned in Section 2.2, only a few cyclotrons currently in use are positive ion machines; the majority are negative ion machines, which eliminates the possibility for alpha or  ${}^3He$  reactions. The energy of the cyclotron determines which nuclear reactions are used to produce radionuclides. A more comprehensive list of potential radionuclides and which type of cyclotron is needed to produce such radionuclides is given in Section 4.

### 2.3.1. Facility considerations

In the case of a low energy cyclotron that accelerates particles in the energy range of up to 12 MeV, shielding may be included with the cyclotron or the cyclotron may be installed inside a vault. The radiation levels around the cyclotron are rather low and with the self-shielding option, the cyclotron can be placed in a normal room. It is still necessary to have an exhaust plan so that any released radioactive gases can be contained. Ozone may also be produced in the vicinity of the cyclotron and this needs to be assessed.

In the energy range of 12–20 MeV, the cyclotron can again be self-shielded or installed inside a vault. If the machine is self-shielded, the shields will typically weigh more than the cyclotron, making floor loading a concern. If the machine is in a vault, the walls need to be more than 1 m thick and made of reinforced concrete. Higher energy cyclotrons need additional shielding, and at energies above 20 MeV the cyclotrons are almost always placed in a vault with concrete walls of up to, and in some cases exceeding, 2 m thickness. Alpha particle machines may require less shielding. A more complete description of facility requirements can be found in IAEA Technical Reports Series No. 471 [4].

### 2.3.2. Nuclear reactions

In general, lower energy cyclotrons will be capable of inducing (p,n) and (p, $\alpha$ ) reactions on low to medium  $Z$  ( $Z < 60$ ) materials. The relative yields of the radionuclides produced with these reactions will be higher with the higher energy systems, but the differences are not large and in some cases, higher energy is undesired due to by-product formation. Comparisons of the energy intervals covered by an 11 MeV cyclotron and a 17 MeV cyclotron are shown in Figs 1 and 2 [1]. Green and pink represent the 11 MeV and 17 MeV machines, respectively. It is important to note that the radioactivity produced is proportional to the area under the curve.

In the example shown in Fig. 1, the amount of  $^{11}\text{C}$  produced at 17 MeV is ~60% higher than at 11 MeV. Correspondingly, the specific activity with the higher energy machine needs to be higher, assuming the amount of target material is the same. The scaling of yields for  $^{18}\text{F}$  is very similar per  $\mu\text{A}$  of beam current between a cyclotron with an energy of 11 MeV and one with an energy of 17 MeV.

‘Non-traditional’ PET radionuclides can be produced on lower energy cyclotrons, but the yields and specific activities are higher with the higher energy machines (as seen in Fig. 2). The nuclear reaction cross-section for  $^{64}\text{Cu}$  is shown in Fig. 2. The portion of the cross-section covered by the higher energy cyclotrons is given in pink, while that of the lower energy systems is given in green. It can be easily seen that the yield with the higher energy cyclotron is about twice that of the lower energy systems. However, it needs to be pointed out that higher energy is not always better. For production of some nuclides (e.g.  $^{68}\text{Ga}$ ,  $^{89}\text{Zr}$ ,  $^{124}\text{I}$ ), a lower energy (e.g. perhaps ~13 MeV) as opposed to the maximum energy of the cyclotron is strategically selected, due to the need to reduce co-production of impurities (e.g.  $^{67}\text{Ga}$ ,  $^{88}\text{Zr}$ ,  $^{123}\text{I}$ , respectively) by the competing (p,2n) reaction, or, in some cases (e.g. considering the  $^{64}\text{Cu}$  described above), to reduce the thickness of the expensive enriched target material. The key to producing as much of the desired radionuclide as possible with minimum impurities is to choose an energy window that best suits the particular nuclear reaction, and the cost of the enriched material if that is used. Using the IAEA Medical Isotope Browser<sup>2</sup> or the National Nuclear Data Center web site<sup>3</sup>, it is possible to look at potential nuclear reactions for production and for reactions that may result in unwanted impurity radionuclides.

In medium energy cyclotrons in the range of 12–20 MeV, it is possible to use some (p,2n) reactions and some additional (p, $\alpha$ ) reactions for higher  $Z$  materials. In high energy cyclotrons of 21–30 MeV, several additional nuclear reactions become possible, including some (p,3n) and (p,pn) reactions. In what are considered here to be very high energy cyclotrons (i.e. 31–70 MeV), reactions of the (p, $xn$ ) type become possible. Nearly every established radionuclide used in nuclear medicine can be produced with these machines, if the energy spread caused by degrading the particle energy can be accepted. It is almost always possible to reduce the energy of the beam coming out of the cyclotron. However, as the energy is reduced, the energy distribution also increases, which raises the possibility of introducing radioisotopic impurities.

Cyclotrons with alpha beams are another category of cyclotron and allow the production of some radionuclides that are not possible to make in a cyclotron in any other way. A prime example of this is the  $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$  reaction. There are also other radionuclides which can be made more conveniently with an alpha beam than with a proton-only machine (e.g.  $^{43}\text{Sc}$ ).

<sup>2</sup> Available at <https://www-nds.iaea.org/relnsd/vcharthtml/VChartHTML.html>

<sup>3</sup> Available at <https://www.nndc.bnl.gov>

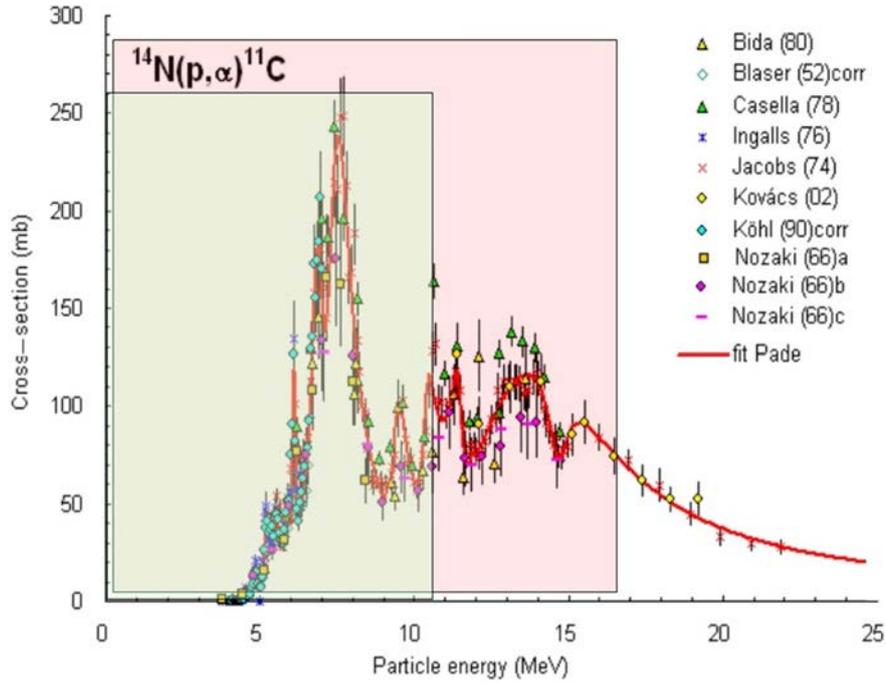


FIG. 1. Cross-section plot for the production of  $^{11}\text{C}$  from the  $^{14}\text{N}(p,\alpha)^{11}\text{C}$  nuclear reaction (adapted from Ref. [1]). Green area: yield from 11 MeV cyclotron. Pink (including green) area: yield from 17 MeV cyclotron.

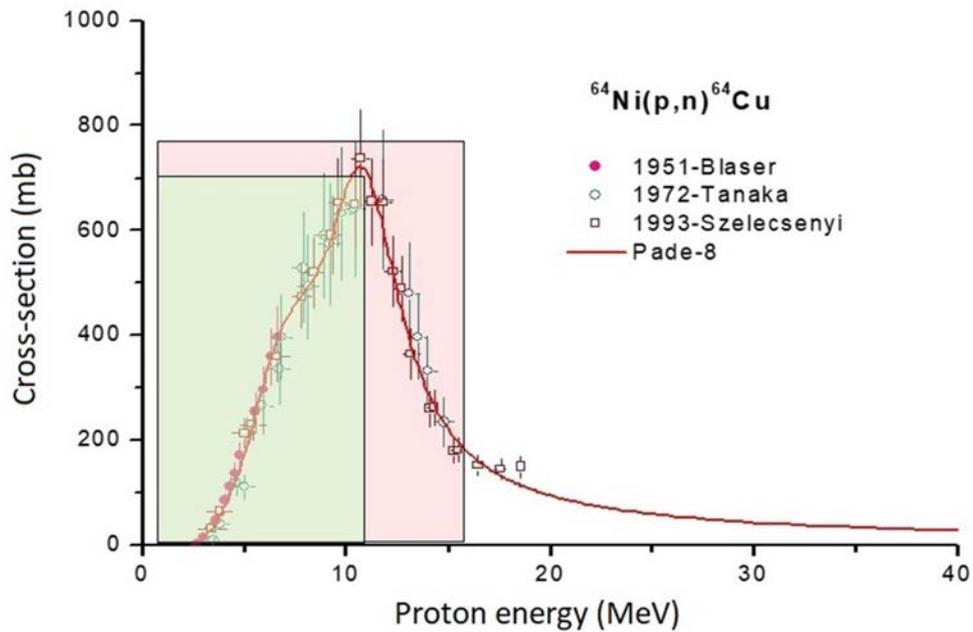


FIG. 2. Cross-section plot for the production of  $^{64}\text{Cu}$  from the  $^{64}\text{Ni}(p,n)^{64}\text{Cu}$  nuclear reaction (adapted from Ref. [1]). Green area: yield from 11 MeV cyclotron. Pink (including green) area: yield from 17 MeV cyclotron.

## 2.4. CYCLOTRON DATABASE

An on-line interactive directory of cyclotrons that are used for radionuclide production in Member States was launched in late 2018 and contains information supplied to the IAEA.<sup>4</sup> This directory was prepared with information collected from reports by major manufacturers and from previous directories. Great efforts were made to include only those cyclotrons in current operation or under testing.

The directory includes a significant number of cyclotrons worldwide that are used, at least in part, for radionuclide production. Some institutions reported that older cyclotrons had been shut down and replaced with newer cyclotrons.

The database is organized alphabetically by Member State and by location, but it can be downloaded and the data sorted in any desired manner. There are individual entries for each cyclotron, even for institutions having more than one cyclotron. The contact person and email address were entered where available. Every effort has been made to update this list, but some of the people listed may have changed positions and may no longer be associated with a particular institution.

There are more than 1300 entries for cyclotrons operating in IAEA Member States. This is an increase of more than 42% compared with the number reported in the 2013 cyclotron directory. The number of cyclotrons has increased in developed countries, but even more so in developing countries. Large concentrations of cyclotrons for radionuclide production are located in the United States of America, Japan and Germany. The single country with the largest number of cyclotrons is the United States of America. However, taken collectively there are more cyclotrons located in East Asia, especially China and Japan, where they are used for medical radionuclide production.

The number of cyclotrons has expanded in the last decade due to advances in medical imaging applications, leading to increased radiopharmaceutical demand worldwide. With the development of sophisticated molecular imaging techniques (PET, SPECT, PET–CT [computed tomography] and PET–MRI [magnetic resonance imaging]), the manufacture of user friendly compact medical cyclotrons has become possible. Furthermore, in many Member States, several PET radiopharmaceuticals are eligible for reimbursement by the government or insurance companies. There is no doubt that the fastest growing segment of the market is in the commercial distribution of 2-<sup>[18F]</sup>fluoro-2-deoxy-D-glucose (<sup>[18F]</sup>FDG) to local hospitals.

The range of commercially available cyclotrons is now quite large and still growing, with beam energies ranging from a few MeV for PET nuclide production only to a few hundred MeV for proton therapy. Cyclotron beam currents range from 40  $\mu\text{A}$  to over 1 mA. The characteristics of commercial cyclotron systems are shown in Table 1.

TABLE 1. LEGACY AND COMMERCIALY AVAILABLE CYCLOTRONS [3]

Manufacturer	Model	Beam energy and current
Best ABT Molecular Imaging	BG-75	7.5 MeV H <sup>+</sup> , 5 $\mu\text{A}$
Advanced Cyclotron Systems (ACSI)	TR-14	11–14 MeV H <sup>-</sup> , 100 $\mu\text{A}$
	TR-19	14–19 MeV H <sup>-</sup> , 300 $\mu\text{A}$
	TR-19/9	19 MeV H <sup>-</sup> , 9 MeV D <sup>-</sup> , 300 $\mu\text{A}$

<sup>4</sup> Available at <https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx>

TABLE 1. LEGACY AND COMMERCIALY AVAILABLE CYCLOTRONS [3] (cont.)

Manufacturer	Model	Beam energy and current
	TR-24	16–24 MeV H <sup>-</sup> , 500 $\mu$ A
	TR-30	30 MeV H <sup>-</sup> , 1000 $\mu$ A
	TR-30/15	30 MeV H <sup>-</sup> , 15 MeV D <sup>-</sup> , 1000 $\mu$ A
CTI (Siemens)	RDS 111	11 MeV H <sup>-</sup> , 60 $\mu$ A
	RDS 112	11 MeV H <sup>-</sup> , 60 $\mu$ A
D.V. Efremov Institute of Electrophysical Apparatus	MGC-20	18 MeV H <sup>-</sup> , 10 MeV D <sup>-</sup> , 160 $\mu$ A
	MCC-30/15	30 MeV H <sup>-</sup> , 15 MeV D <sup>-</sup> , 350 $\mu$ A
	CC-18/9	18 MeV H <sup>-</sup> , 9 MeV D <sup>-</sup> , 150 $\mu$ A
	CC-12	12 MeV H <sup>-</sup> , 60 $\mu$ A
General Electric	GENtrace	7.8 MeV H <sup>-</sup> , 50 $\mu$ A
	MINItrace	9.6 MeV H <sup>-</sup> , 70 $\mu$ A
	PETtrace	16.5 MeV H <sup>-</sup> , 160 $\mu$ A, 8.4 MeV D <sup>-</sup> , 60 $\mu$ A
Ion Beam Applications	Cyclone 3	3.8 MeV D <sup>-</sup> , 60 $\mu$ A
	Cyclone 10/5	10 MeV H <sup>-</sup> , 5 MeV D <sup>-</sup> , 60 $\mu$ A
	Cyclone 18/9	18 MeV H <sup>-</sup> , 9 MeV D <sup>-</sup> , 80 $\mu$ A
	Cyclone 18+	18 MeV H <sup>-</sup> , 80 $\mu$ A
	Cyclone Kiube	18 MeV H <sup>-</sup> , 300 $\mu$ A
	Cyclone Kiube VE	18 MeV H <sup>-</sup> , 300 $\mu$ A
	Cyclone 30	30 MeV H <sup>-</sup> , 15 MeV D <sup>-</sup> , 400 $\mu$ A
	Cyclone 235	240 MeV H <sup>-</sup>
Japan Steel Works	BC168	16 MeV H <sup>+</sup> , 8 MeV D <sup>+</sup> , 50 $\mu$ A
	BC1710	17 MeV H <sup>+</sup> , 10 MeV D <sup>+</sup> , 60 $\mu$ A
	BC2010N	20 MeV H <sup>-</sup> , 10 MeV D <sup>-</sup> , 60 $\mu$ A
	BC2211	22 MeV H <sup>+</sup> , 11 MeV D <sup>+</sup> , 60 $\mu$ A
	BC3015	30 MeV H <sup>+</sup> , 15 MeV D <sup>+</sup> , 60 $\mu$ A
Oxford Instruments	OSCAR 12	12 MeV H <sup>-</sup> , 60 $\mu$ A

TABLE 1. LEGACY AND COMMERCIALY AVAILABLE CYCLOTRONS [3] (cont.)

Manufacturer	Model	Beam energy and current	
Samyoung Unitech	KOTRON-13	13 MeV H <sup>+</sup> , 100 μA	
Scanditronix Magnet AB	MC17	17.2 MeV H <sup>+</sup> , 8.3 MeV D <sup>+</sup> , 60 μA 12 MeV 3He <sup>++</sup> , 16.5 4He <sup>++</sup> , 60 μA	
	MC30	30 MeV H <sup>+</sup> , 15 MeV D <sup>+</sup> , 60 μA	
	MC32NI	15–32 MeV H <sup>-</sup> , 8–16 MeV D <sup>-</sup> , 60 μA 11–23 MeV 3He <sup>++</sup> , 15–31 4He <sup>++</sup> , 60 μA	
	MC40	10–40 MeV H <sup>+</sup> , 5–20 MeV D <sup>+</sup> , 60 μA 13–53 MeV 3He <sup>++</sup> , 10–40 4He <sup>++</sup> , 60 μA	
	MC50	18–52 MeV H <sup>+</sup> , 9–25 MeV D <sup>+</sup> , 60 μA 24–67 MeV 3He <sup>++</sup> , 18–50 4He <sup>++</sup> , 60 μA	
	MC60	50 MeV H <sup>+</sup> , 60 μA	
	K130	6–90 MeV H <sup>-</sup> , 10–65 MeV D <sup>-</sup> , 60 μA 16–173 MeV 3He <sup>++</sup> , 20–130 4He <sup>++</sup>	
	Sumitomo Heavy Industries	CYPRIS 325	16 MeV H <sup>+</sup> , 8 MeV D <sup>+</sup> , 60 μA
		CYPRIS 370	16 MeV H <sup>+</sup> , 10 MeV D <sup>+</sup> , 60 μA
		HM-12	12 MeV H <sup>-</sup> , 6 MeV D <sup>-</sup> , 60 μA
HM-18		18 MeV H <sup>-</sup> , 10 MeV D <sup>-</sup> , 60 μA	
480 AVF		30 MeV H <sup>+</sup> , 60 μA	
AVF 680		40 MeV H <sup>+</sup> , 60 μA	
AVF 715		50 MeV H <sup>+</sup> , 60 μA	
AVF 750		70 MeV H <sup>+</sup> , 60 μA	
AVF 930		90 MeV H <sup>+</sup> , 60 μA	
AVF 1000		80 MeV H <sup>+</sup> , 60 μA	
Ring Cyclotron 400		400 MeV H <sup>+</sup> (K = 400), 60 μA	
Ring Cyclotron 540		240 MeV H <sup>+</sup> (K = 540), 60 μA	
C235		240 MeV H <sup>-</sup> , 60 μA	

## 3. CYCLOTRON TARGETRY

### 3.1. GENERAL CONSIDERATIONS

The goal of cyclotron targetry is to get the target material into the beam, keep it there during irradiation and remove the produced radionuclide from the target material quickly and efficiently after irradiation, preferably with some level of automation to reduce personnel dose. Unless the design of the target is well matched to the characteristics of the cyclotron, the production of radionuclides can be far from optimal. The design of targets associated with one cyclotron may not be optimal for a different cyclotron. Besides the characteristics of mechanical design, beam energy and beam current, the major variables that impact on target design are the beam size and profile. There are often significant differences in the characteristics of the beam profile between a positive ion cyclotron and a negative ion cyclotron, for example. The negative ion cyclotron usually has a more uniform beam profile incident on the target. This is a result of the extraction process through a stripping foil, which tends to eliminate hot spots in the beam [5–7]. Focusing magnets and steering magnets along the transport line, if there is one, can alter the beam to a more homogeneous shape. The positive ion cyclotron may have a uniform beam profile, or the profile may be quite ‘hot’ in spots and not uniform at all, depending on the extraction characteristics and focusing magnets used to transport the beam. In general, the extraction process for positive ions tends to create areas of high intensity particles in the beam.

Most of the newer, commercially available cyclotrons are negative ion cyclotrons and have targets mounted directly on the cyclotron without any focusing or steering magnets to alter the beam shape. While this concept is acceptable for liquid and gaseous targets, the fact that there is no possibility to alter the beam profile may be a challenge for the irradiation of solid targets with low heat conductivity, while hot spots in the beam can damage or even destroy the irradiated material.

Manufacturers will usually provide targets that are well suited to their cyclotron, but they are designed for radionuclides that are more commonly produced such as  $^{18}\text{F}$ ,  $^{11}\text{C}$  or  $^{123}\text{I}$ . Targets for the production of the alternative radionuclides described in this publication often have very different physical and chemical characteristics from the more common ones. For this reason, it is important to understand some of the basic principles involved in target design [8]. A more comprehensive discussion of this subject can be found in other IAEA publications series [2, 3, 9].

### 3.2. TARGET TYPES

Gases, liquids or solids may be used as target materials for the production of radionuclides depending on the particular radioisotope being produced. Targets are, consequently, designed to accommodate the material being irradiated. The design of the target will also depend on whether the target is placed inside (internal) or outside (external) the cyclotron.

When irradiating a gaseous target material, the targets are usually of cylinder or capsule form to hold the gas under pressure. A thin beam entry foil allowing the projectile to penetrate the target is usually referred to as a window. Cooling is a major issue for gas targets, since gases are weak heat conductors and compared with solids or liquids need more volume to reach the same irradiated mass of target material. A schematic diagram of a typical gas target is shown in Fig. 3 [3].

The temperature inside the target will affect the product distribution. The effect of temperature on the density reduction can be very high, depending on the beam current (or the total power delivered to the gas). Temperatures inside a gas target can be several hundred degrees Celsius. In the case of liquids, the target material occupies a specific volume unless the liquid volatilizes. The liquid is typically added to

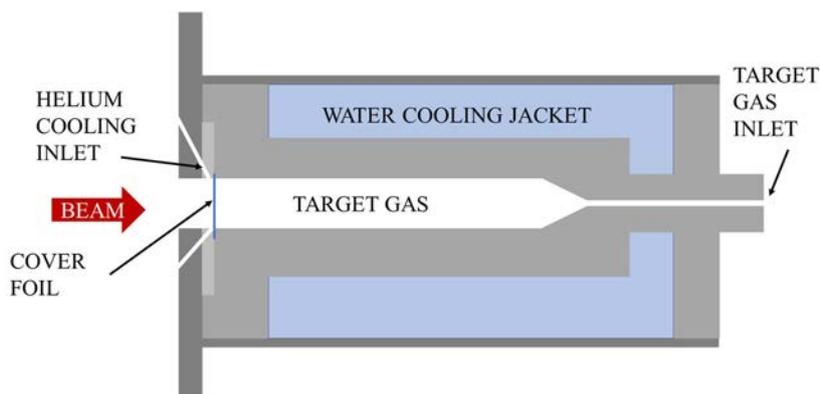


FIG. 3. Schematic diagram of a typical gas target (adapted from Ref. [3]).

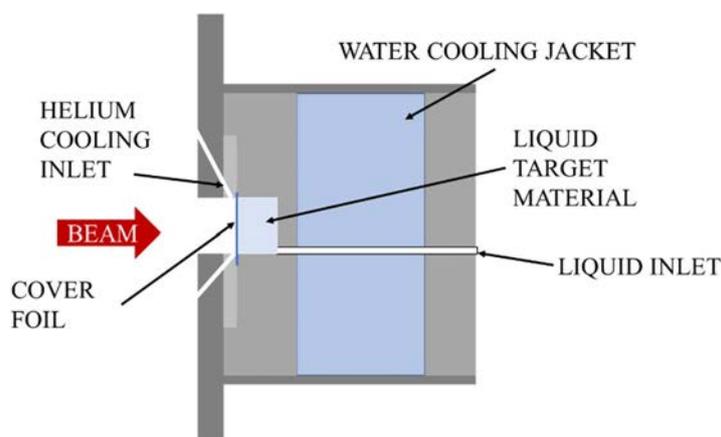


FIG. 4. Schematic diagram of a typical liquid target (adapted from Ref. [3]).

and removed from the target remotely with the target affixed to the cyclotron. A typical liquid target for the production of  $^{18}\text{F}$  from  $^{18}\text{O}$  in water is shown in Fig. 4 [3].

During normal production conditions, the water reaches the boiling point and stays at that temperature during the irradiation. The boiling point of the water may be increased by pressurizing the target. When the target is boiling, the production of the radionuclides is lower than if the target remains liquid. This assumes that the range of the particles at these energies in the target is similar to the dimensions of the target cavity. By making the target much longer than the dimensions of the particle path, yield while boiling can be increased. This technique has been used on several commercial targets, in which observations show that density reduction is at work in nearly all gaseous and liquid targets to one extent or another and yields can be increased by compensating for this phenomenon.

Because the density of solids is typically higher than that of liquids or gases, the path length of the beam is shorter and the target considerably smaller. The solid can be in many forms (e.g. foil, powder, electroplated, melted, vapour deposited, etc.). If the solid is a good heat conductor, the beam can typically be perpendicular to the solid. A typical solid target for conductive powders is shown in Fig. 5.

If the material is very expensive (e.g. highly enriched isotopes) or if the material is a poor heat conductor, the power density can be decreased by using an inclined plane target with a thinner layer as shown in Fig. 6.

For most solid targets, the best method for producing targets that will withstand high beam currents and yet are easy to process is electroplating. Good thermal contact between the target material and the cooling plate allows beam currents to be higher. By using electrochemical processing and recovery of the material, the processing is greatly simplified [10–12]. There are two major reasons to use targets that have

been enriched in a particular isotope. First, the target may use isotopically enriched material to produce more of the isotope of interest. Second, the use of the natural abundance target element may result in the production of unwanted side products. The major difficulties with using enriched materials is that they can be very expensive and they may not be available easily. Typically, enriched target material is recycled for use in future targets.

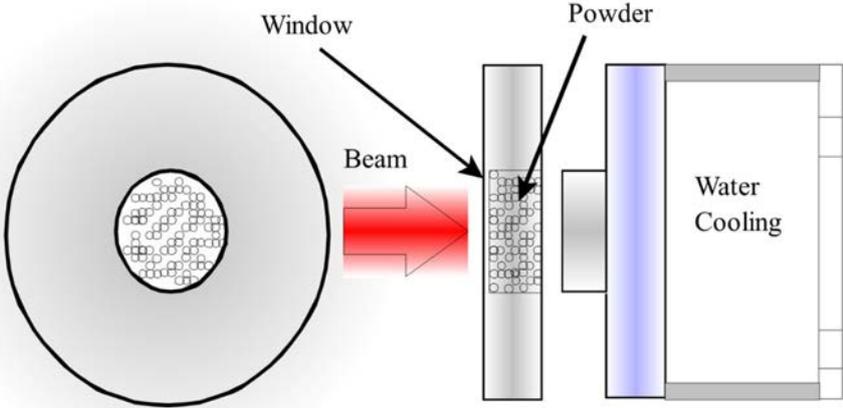


FIG. 5. Schematic diagram of a typical solid target using a powdered material (reproduced from Ref. [3]).

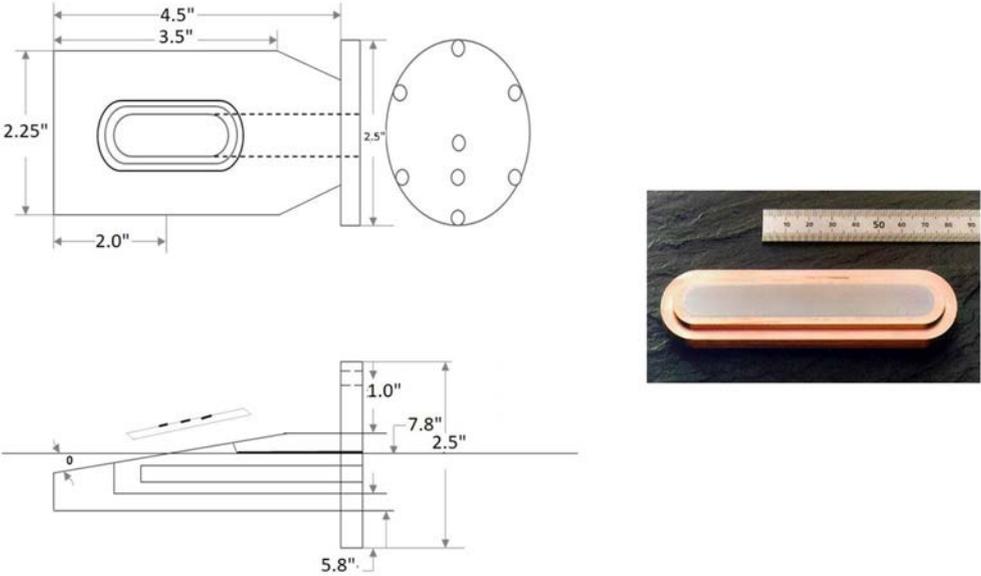


FIG. 6. Left: Schematic diagram of an inclined plane target with electroplated target material (reproduced from Ref. [3]). Right: An electroplated solid target on a copper backing.

## 4. CYCLOTRON BASED ALTERNATIVE RADIONUCLIDE PRODUCTION

### 4.1. OVERVIEW

There is significant potential at facilities with cyclotrons for the production and development of alternative radionuclides and new radiopharmaceuticals, other than traditional PET radionuclides such as  $^{18}\text{F}$ ,  $^{11}\text{C}$ ,  $^{15}\text{O}$  and  $^{13}\text{N}$ . Table 2 provides a list of these potential radionuclides. The nuclear reactions listed in this table represent the most common methods of production. The remainder of this section briefly describes the potential radionuclide production routes using cyclotrons in different energy ranges. It also provides guidelines and methods for developing targets and the chemistry for the separation of radionuclides from target materials, as well as a large number of references to relevant literature. Optimal separation techniques for cyclotron based radionuclides are also essential to achieve high specific activity and chemical purity suitable for radiopharmaceutical production.

*Text cont. on p. 20.*

TABLE 2. POTENTIAL CYCLOTRON BASED RADIONUCLIDES OTHER THAN TRADITIONAL PET RADIONUCLIDES [1]

Element	Product nuclide	Half-life <sup>a</sup>	Nuclear reaction <sup>b</sup>	Q value <sup>c</sup> (MeV)	Practical energy range <sup>d</sup> (MeV)	Particle energy <sup>e</sup> (MeV)				Comments <sup>f</sup>
						<12	12–20	21–30	30+	
Actinium	Ac-225	10 d	$^{226}\text{Ra}(p,2n)$	-6.85	25–8.0	n.a. <sup>g</sup>	x	x	n.a.	
Antimony	Sb-117	2.8 h	$^{117}\text{Sn}(p,n)^*$	-2.54	13–2.6	x	x	n.a.	n.a.	Upper energy may be limited depending on the enrichment
	Sb-119	38.2 h	$^{119}\text{Sn}(p,n)^*$	-1.37	11–4	x	n.a.	n.a.	n.a.	
Arsenic	As-72	26 h	$^{72}\text{Ge}(p,n)^*$	-5.14	13.8–5.2	x	x	n.a.	n.a.	
	As-76	1.09 d	$^{76}\text{Ge}(p,n)^*$	-1.70	16–2	x	x	n.a.	n.a.	
Astatine	At-211	7.2 h	$^{209}\text{Bi}(\alpha,2n)$	-20.3	28.6–21.0	n.a.	n.a.	x	n.a.	
Bismuth	Bi-213	45.6 min	$^{226}\text{Ra}(p,2n)^*$ decay	-6.85	25–8.0	n.a.	x	x	n.a.	
Bromine	Br-75	1.6 h	$^{76}\text{Se}(p,2n)^*$	-14.99	27.2–19	–	–	x	n.a.	
	Br-76	16.2 h	$^{76}\text{Se}(p,n)^*$	-5.74	16–6	x	x	n.a.	n.a.	
	Br-77	2.37 d	$^{77}\text{Se}(p,n)$	-2.15	28–13	x	x	x	n.a.	
	Br-80	4.42 h	$^{78}\text{Se}(p,2n)^*$	-12.64	16–3	x	x	n.a.	n.a.	
Calcium	Ca-47	4.54 d	$^{48}\text{Ca}(p,pn)^*$	-9.95	70–10	–	x	x	x	
Cobalt	Co-55	17.53 h	$^{58}\text{Ni}(p,\alpha)^*$	-1.3	11–8	x	n.a.	n.a.	n.a.	

TABLE 2. POTENTIAL CYCLOTRON BASED RADIONUCLIDES OTHER THAN TRADITIONAL PET RADIONUCLIDES [1] (cont.)

Element	Product nuclide	Half-life <sup>a</sup>	Nuclear reaction <sup>b</sup>	Q value <sup>c</sup> (MeV)	Practical energy range <sup>d</sup> (MeV)	Particle energy <sup>e</sup> (MeV)				Comments <sup>f</sup>
						<12	12–20	21–30	30+	
Copper	Co-58m	9.1 h	$^{58}\text{Fe}(p,n)^*$	+2.84	20–2	x	x	n.a.	n.a.	
			$^{57}\text{Fe}(d,n)^*$	+4.73	20–2	x	x	n.a.	n.a.	
	Cu-60	23.7 min	$^{60}\text{Ni}(p,n)^*$	-6.91	27–4	x	x	x	n.a.	
Copper	Cu-61	3.35 h	$^{61}\text{Ni}(p,n)^*$	-3.02	15–3	x	x	n.a.	n.a.	$^{60}\text{Cu} \sim 9\%$
			$^{60}\text{Ni}(d,n)$	+2.57	13–3	x	n.a.	n.a.	n.a.	
			$^{64}\text{Zn}(p,\alpha)^*$	+0.80	20–5	x	x	n.a.	(x)	
	Cu-64	12.7 h	$^{67}\text{Zn}(p,\alpha)^*$	+2.41	30–4	x	x	x	(x)	
			$^{66}\text{Zn}(d,\alpha)^*$	+7.24	20–4	x	x	x	(x)	
			$^{64}\text{Ni}(p,n)$	-2.46	20–2.5	n.a.	n.a.	n.a.	n.a.	Entrance energy needs to be below 13 MeV to avoid radiocobalt impurities
Erbium	Cu-67	2.6 d	$^{70}\text{Zn}(p,\alpha)^*$	+2.62	25–5	x	x	x	(x)	
			$^{64}\text{Ni}(\alpha,p)^*$	-4.64	28–10	–	x	x	n.a.	
Erbium	Er-165	10.36 h	$^{165}\text{Ho}(p,n)$	-1.16	30–5	x	x	x	x	
Gallium	Ga-66	9.49 h	$^{66}\text{Zn}(p,n)^*$	-5.96	18–6	x	x	x	n.a.	

TABLE 2. POTENTIAL CYCLOTRON BASED RADIONUCLIDES OTHER THAN TRADITIONAL PET RADIONUCLIDES [1] (cont.)

Element	Product nuclide	Half-life <sup>a</sup>	Nuclear reaction <sup>b</sup>	Q value <sup>c</sup> (MeV)	Practical energy range <sup>d</sup> (MeV)	Particle energy <sup>e</sup> (MeV)				Comments <sup>f</sup>
						<12	12–20	21–30	30+	
Gallium	Ga-67	3.2 d	$^{68}\text{Zn}(p,2n)$	-11.98	30–12	–	x	x	n.a.	
	Ga-68	68 min	$^{68}\text{Zn}(p,n)^*$	-3.70	18–4	x	x	n.a.	n.a.	
Germanium	Ge-68	270.9 d	$^{69}\text{Ga}(p,2n)^*$	-11.20	30–12	–	x	x	n.a.	
Indium	In-110m	69 min	$^{110}\text{Cd}(p,n)^*$	-4.66	18–5	x	x	n.a.	n.a.	
	In-111	2.8 d	$^{111}\text{Cd}(p,n)^*$	-1.64	18–5	x	x	n.a.	n.a.	
			$^{112}\text{Cd}(p,2n)^*$	-11.04	30–12	–	x	x	n.a.	Higher yield than on $^{111}\text{Cd}(p,n)$
Iodine	I-121	2.12 h	$^{122}\text{Te}(p,2n)^*$	-12.92	30–13	–	x	x	n.a.	
	I-123	13.3 h	$^{124}\text{Te}(p,2n)^*$	-11.44	30–18	–	n.a.	x	n.a.	$^{124}\text{I}$ production is unavoidable
			$^{123}\text{Te}(p,n)$	-2.01	19–5	x	n.a.	n.a.	n.a.	
	I-124	4.2 d	$^{124}\text{Te}(p,n)^*$	-3.94	11.5–4.5	x	n.a.	n.a.	n.a.	
Iron	Fe-52	8.3 h	$^{50}\text{Cr}(a,2n)$	-15.65	45–17	–	–	x	n.a.	$^{55}\text{Fe}$ is co-produced
Manganese	Mn-52	5.59 d	$^{52}\text{Cr}(p,n)$	-5.49	20–6	x	x	n.a.	n.a.	$^{54}\text{Mn}$ contamination if natural target is used
			$^{52}\text{Cr}(d,2n)$	-7.72	25–8	(x)	x	x	n.a.	Higher yield than for (p,n)

TABLE 2. POTENTIAL CYCLOTRON BASED RADIONUCLIDES OTHER THAN TRADITIONAL PET RADIONUCLIDES [1] (cont.)

Element	Product nuclide	Half-life <sup>a</sup>	Nuclear reaction <sup>b</sup>	Q value <sup>c</sup> (MeV)	Practical energy range <sup>d</sup> (MeV)	Particle energy <sup>e</sup> (MeV)				Comments <sup>f</sup>
						<12	12–20	21–30	30+	
Molybdenum	Mo-99	65.9 h	<sup>100</sup> Mo(p,pn)*	-8.29	70–10	-	-	x	x	x
Niobium	Nb-90	14.6 h	<sup>90</sup> Zr(p,n)*	-6.89	17.2–7	x	x	n.a.	n.a.	n.a.
Palladium	Pd-103	17.0 d	<sup>103</sup> Rh(p,n)	-1.35	15–5	x	x	n.a.	n.a.	n.a.
Platinum	Pt-191	2.8 d	<sup>191</sup> Ir(p,n)*	-1.79	5–70	(x)	x	x	x	x
Rhenium	Re-186	90.6 h	<sup>186</sup> W(p,n)*	-1.36	15.3–5	x	x	n.a.	n.a.	n.a.
Scandium	Sc-43	3.89 h	<sup>44</sup> Ca(p,2n)*	-14.13	30–16.7	-	(x)	x	n.a.	n.a.
			<sup>43</sup> Ca(p,n)*	-3.00	18–3	x	x	n.a.	n.a.	Preferred p reaction. Similar yield as for <sup>43</sup> Ca+d
			<sup>42</sup> Ca(d,n) <sup>43</sup> Sc*	-2.70	3–18	x	x	n.a.	n.a.	n.a.
			<sup>43</sup> Ca(d,2n) <sup>43</sup> Sc*	-5.23	30–8	x	x	x	n.a.	Higher yield is expected than for <sup>42</sup> Ca+d
			<sup>40</sup> Ca(a,p) <sup>43</sup> Sc	-3.52	25–5	x	x	x	n.a.	Highest yield, natural Ca
	Sc-44	3.93 h	<sup>44</sup> Ca(p,n)*	-4.44	14.5–4.5	x	x	n.a.	n.a.	n.a.
	Sc-47	3.35 d	<sup>48</sup> Ca(p,2n)*	-8.74	20–16	-	x	n.a.	n.a.	n.a.
			<sup>44</sup> Ca(a,p) <sup>47</sup> Sc*	-2.00	15–6	x	x	n.a.	n.a.	n.a.

TABLE 2. POTENTIAL CYCLOTRON BASED RADIONUCLIDES OTHER THAN TRADITIONAL PET RADIONUCLIDES [1] (cont.)

Element	Product nuclide	Half-life <sup>a</sup>	Nuclear reaction <sup>b</sup>	Q value <sup>c</sup> (MeV)	Practical energy range <sup>d</sup> (MeV)	Particle energy <sup>e</sup> (MeV)				Comments <sup>f</sup>
						<12	12–20	21–30	30+	
			<sup>48</sup> Ti(p,2p)	-11.44	n.a.	n.a.	x	x	n.a.	n.a.
			<sup>50</sup> Ti(p,a)	-2.23	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Strontium	Sr-82	25.5 d	<sup>85</sup> Rb(p,4n) <sup>82</sup> Sr*	-31.15	70–31.6	–	–	–	x	x
Technetium	Tc-94m	52 min	<sup>94</sup> Mo(p,n)*	-5.04	13.8–5.5	x	x	n.a.	n.a.	n.a.
	Tc-99m	6.01 h	<sup>100</sup> Mo(p,2n)*	-7.72	25–10	x	x	n.a.	n.a.	If the specific activity is important, upper energy limit is 24 MeV
Terbium	Tb-149	4.12 h	<sup>152</sup> Gd(p,4n) <sup>149</sup> Tb*	-28.21	28.5–50	–	–	–	x	Co-production of <sup>150,151,152</sup> Tb is unavoidable
Thallium	Tl-201	72.9 h	<sup>203</sup> Tl(p,3n) <sup>201</sup> Pb*	-17.42	24.5–20	–	–	x	(x)	Exit energy below 22–23 MeV can result in <sup>202</sup> Tl impurity
Tin	Sn-117m	13.9 d	<sup>114</sup> Cd(α,n)*	-5.26	30–6	(x)	x	x	x	n.a.
Titanium	Ti-44	59.1 y	<sup>45</sup> Sc(p,2n)	-12.38	50–13	–	(x)	x	x	x
	Ti-45	184.8 min	<sup>45</sup> Sc(p,n)	-2.84	20–3	x	x	x	x	n.a.
Yttrium	Y-86	14.7 h	<sup>86</sup> Sr(p,n)*	-6.02	15.8–6.1	x	x	n.a.	n.a.	n.a.

TABLE 2. POTENTIAL CYCLOTRON BASED RADIONUCLIDES OTHER THAN TRADITIONAL PET RADIONUCLIDES [1] (cont.)

Element	Product nuclide	Half-life <sup>a</sup>	Nuclear reaction <sup>b</sup>	Q value <sup>c</sup> (MeV)	Practical energy range <sup>d</sup> (MeV)	Particle energy <sup>e</sup> (MeV)			Comments <sup>f</sup>
						<12	12–20	21–30	
Zinc	Zn-62	9.2 h	<sup>63</sup> Cu(p,2n)*	-13.26	35–14		x	x	n.a.
	Zn-63	38.5 min	<sup>63</sup> Cu(p,n)*	-4.15	20–5	x	x	n.a.	n.a.
Zirconium	Zr-89	78.4 h	<sup>89</sup> Y(p,n)	-3.6	14–4	x	x	n.a.	Co-production of <sup>88</sup> Zr occurs at $E > 14$ MeV

<sup>a</sup> y: years; d: days; h: hours; min: minutes.

<sup>b</sup> Reaction under consideration; \*: use of a particular isotope. Other isotopes of the element may produce other radionuclides and enriched isotopes may be necessary.

<sup>c</sup> Negative numbers mean an endoergic reaction; positive numbers mean an exoergic reaction.

<sup>d</sup> Values correspond to the energy range in which the named isotopes can be made, but without limits imposed by production of radionuclidic impurities.

<sup>e</sup> x: the radionuclide can be made on a cyclotron with the energy listed. Radionuclides can be made on higher energy machines, but usually require degrading the energy, which may introduce impurities due to the distribution of energies created with beam energy degradation;

(x): the reaction at higher energy is limited due to the cost of the enriched isotope;

–: no experiments have taken place for this item.

<sup>f</sup> Comments on the particular reaction may include the energies at which impurities may interfere or the energy window due to economic factors.

<sup>g</sup> n.a.: not applicable.

## 4.2. ACTINIUM-225

One of the biggest problems in the management of cancer is the control of metastatic disease. The ideal therapy is one that is active only in the cancer cell and not in nearby normal cells. Alpha emitting radioisotopes, having a short path length and high energy transfer, can be more effective in killing nearby cancer cells than beta emitting radioisotopes, which have a somewhat longer path length and lower energy transfer [13]. Alpha therapeutics have properties that are particularly suited for the elimination of single cells in transit or small nests of cancer cells, since they have a high rate of energy loss and short range and are not the best to treat solid tumours, for which beta radioisotopes are much better suited. An advantage of  $^{225}\text{Ac}$  is that the decay chain results in four alpha particles being emitted in a short period of time (Fig. 7). Promising biochemical responses to  $^{225}\text{Ac}$  radiotherapeutics in patients who are resistant to beta-particle radiation illustrate the potential of targeted alpha therapy for the treatment of certain types of cancer. In order to be the most effective, with a targeting moiety of high affinity and specificity for the tumour, there must be a radionuclide with the desired physical properties. An appropriate linker moiety to consistently produce a stable conjugate that remains intact in the face of human catabolism is necessary [14–16].

TABLE 3. PROPERTIES OF ACTINIUM-225 [1]

Isotope	Half-life	Decay mode	Highest abundance alpha energy	Nuclear reaction	Comments
Ac-225	9.9203 d	Alpha emission (see Fig. 7)	5.83 MeV	$^{226}\text{Ra}(p,2n)$	Used only for therapy

### 4.2.1. Production parameters

While several production paths are possible, the cyclotron based reaction for the production of  $^{225}\text{Ac}$  is via the proton induced reaction on  $^{226}\text{Ra}$ :  $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$  (Table 3) is favourable, considering that  $^{226}\text{Ra}$  is available (e.g. brachytherapy sources) and holders are trying to dispose of it due to the complications and costs of storing it for extremely long periods of time (the half-life of  $^{226}\text{Ra}$  is 1600 years). The primary impurity in the production of this radionuclide is the  $^{226}\text{Ra}(p,n)^{226}\text{Ac}$  reaction. This impurity has a 29.4 hour half-life and can be allowed to decay out. The cross-section of this reaction has not been directly measured but is expected to be higher at lower energies. This sets the optimum energy window for the production of  $^{225}\text{Ac}$ . The other potential impurity is the  $^{227}\text{Ac}$  from the  $^{226}\text{Ra}(p,\gamma)^{227}\text{Ac}$  reaction, which is only an issue at high energies. Handling of the radium target and the radon produced during decay are real safety concerns, and careful planning and technical controls are essential.

### 4.2.2. Targetry and separation chemistry

Several types of targets have been used to produce  $^{225}\text{Ac}$ . The initial targets were radium nitrate salt deposited on an aluminium disc, which allowed quick dissolution of the target material but resulted in low yields due to the low abundance of radium in the target material. Later targets were prepared by electroplating radium onto a copper plate, but these were limited by the thickness of the radium layer. Separation of the actinium from the other elements produced during the irradiation has been reported from Karlsruhe using Eichrom resins. DOWEX 1X8 has also been used to separate the actinium and radium from the other products produced in the nuclear reactions. The actinium was separated from the radium with a DOWEX 50WX8 resin. Once this separation had been carried out, the actinium was allowed to decay until the  $^{226}\text{Ac}$  had decayed out, and the resulting  $^{225}\text{Ac}$  was loaded into a cartridge used as the  $^{213}\text{Bi}$  generator. A more efficient scheme was also worked out using Eichrom supported materials and

hydrochloric acid (HCl) to dissolve the target. These modified resins are highly selective extraction media fixed onto mostly inorganic carriers. The method using these resins seems to give a better separation in less time than the DOWEX resins (Fig. 8). The recovery of the radium needs to be done just before the preparation of the targets.

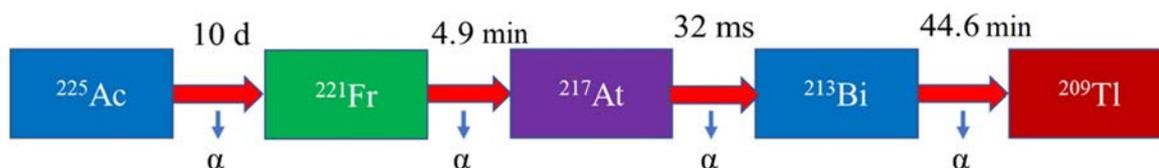


FIG. 7. Decay scheme of  $^{225}\text{Ac}$ .

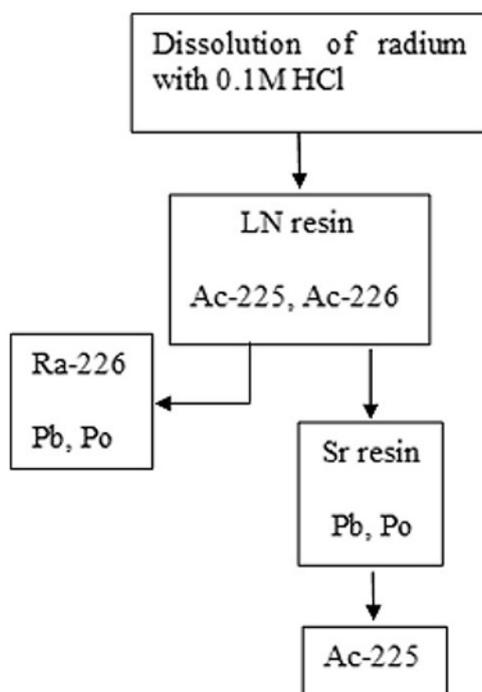


FIG. 8. Improved separation of  $^{225}\text{Ac}$  from radium with Eichrom resins.

### 4.3. ANTIMONY

The isotopes  $^{117}\text{Sb}$  and  $^{119\text{g}}\text{Sb}$  have been suggested as a theranostic pair for imaging (SPECT) and therapy (Auger electron), respectively. However, other than a handful of publications, research efforts regarding the production or application of either of these isotopes have not been extensive [17–19].

TABLE 4. PROPERTIES OF ANTIMONY [17, 18]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Sb-117	2.80 h	$\beta^+$ (1.81%) $\beta^+_{\text{mean}} = 262 \text{ keV}$	158.562 keV (85.9%)	$^{117}\text{Sn}(p,n)^{117}\text{Sb}$
Sb-119g	38.19 h	EC (100%)	23.870 keV (16.50%)	$^{119}\text{Sn}(p,n)^{119}\text{Sb}$

#### 4.3.1. Production parameters

The isotopes  $^{117}\text{Sb}$  and  $^{119\text{g}}\text{Sb}$  can be produced by proton irradiation of tin via the  $^{117}\text{Sn}(p,n)^{117}\text{Sb}$  ( $E_{\text{th}} = 2.562 \text{ MeV}$ ) and  $^{119}\text{Sn}(p,n)^{119}\text{Sb}$  ( $E_{\text{th}} = 1.384 \text{ MeV}$ ) reactions, respectively (Table 4). Both excitation functions are similar, presenting maximum yields between  $\sim 15\text{--}8 \text{ MeV}$  with a maximum of 600–800 mb [18, 20]. For radioisotopically pure production of either isotope, enriched tin is used. To reduce the amount of co-produced  $^{116}\text{Sb}$  and  $^{118}\text{Sb}$ , the proton energy needs to be limited to around 13 and 11 MeV, respectively. With the goal of increasing ease of distribution of  $^{119}\text{Sb}$ , production of the longer lived  $^{119\text{m}}\text{Te}$  ( $T_{1/2} = 4.70 \text{ d}$ ), which in turn decays to  $^{119}\text{Sb}$ , has recently been investigated by high energy (42.5 MeV) proton irradiation of  $^{\text{nat}}\text{Sb}$  targets [19].

#### 4.3.2. Targetry and separation chemistry

Targets can be prepared from electroplated isotopically enriched tin on silver backings [17]. After irradiation, the tin can be dissolved in hot concentrated HCl with hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and the radioantimony purified by weak anion exchange resin separation (AG4-X4), eluted with 0.8M HCl [18]. If enriched tin is used, the target material is recycled.

### 4.4. ARSENIC

Arsenic radioisotopes are of considerable interest in the field of nuclear medicine because of their unique nuclear and chemical properties, which make them well suited for theranostic radiopharmaceuticals. The success of arsenic trioxide for the treatment of certain types of lymphomas has resulted in the development of arsenic-containing small molecules and drug delivery vehicles to mitigate systemic toxicity and allow for arsenic based treatments for other cancer indications [21]. Arsenic has also been used to treat acute promyelocytic leukaemia [22]. The biological activity of trivalent arsenic is largely due to its high sulphur affinity allowing for its covalent binding to thiol/sulphydryl groups, such as cysteine side chains. These chemical and biochemical properties make radioarsenic ideal as both a diagnostic PET labelled arsenic based chemotherapy agent and a biological targeting vector through the use of covalent arsenic-thiol linkages to radiolabel the molecules. Trithiol chelates are suitable to be used for potential theranostic radiopharmaceuticals. A bifunctional trithiol chelate has been developed and conjugated to bombesin (7–14) $\text{NH}_2$  as a model peptide to investigate the in vivo stability of trithiol chelates complexed with no carrier added radioarsenic [23].

TABLE 5. PROPERTIES OF ARSENIC [24–26]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
As-72	26 h	$\beta^+$ (88%) EC (12%) $\beta_{\text{mean}}^+ = 1.17$ MeV	833.99 keV (81%)	$^{72}\text{Ge}(p,n)$
As-76	26.24 h	$\beta^-$ (100%) $\beta_{\text{mean}}^- = 1.06$ MeV	559.1 keV (59%)	$^{76}\text{Ge}(p,n)$

#### 4.4.1. Production parameters

Arsenic-72 can be produced directly by irradiation of germanium [24] or from a  $^{72}\text{Se}/^{72}\text{As}$  generator (Table 5) [25, 26]. Regarding the generator, the  $^{72}\text{Se}$  was produced by a high energy proton (100 MeV) irradiation of natural bromine [26] or alpha particle irradiation (47.3 MeV) on  $^{70}\text{Ge}$  metal powder [27]. The  $^{72}\text{Se}$  could also potentially be produced by the alpha irradiation of enriched  $^{70}\text{Ge}$ .

In the direct production of  $^{72}\text{As}$ , an enriched germanium target was produced by the reduction of  $\text{GeO}_2$  with hydrogen. This metallic germanium was irradiated to produce  $^{72}\text{As}$  via the  $^{72}\text{Ge}(p,n)^{72}\text{As}$  reaction using a beam energy of 16 MeV and a beam current of 20  $\mu\text{A}$  [24].

#### 4.4.2. Targetry, irradiation parameters and separation chemistry

In terms of the generator chemistry for  $^{72}\text{As}$ , a radiochemical separation scheme has been developed that ensures high selectivity and radionuclidic purity of the separated arsenic fraction. A series of resins were used and were very effective in separating the arsenic from the selenium (IV). Arsenic was easily eluted from the columns and more than 95% of the total amount of arsenic was eluted in the first 2 mL of both 0.9% and 2.5% sodium chloride (NaCl) solutions [25].

In the processing step for the direct production of  $^{72}\text{As}$ , the irradiated [ $^{72}\text{Ge}$ ]GeO<sub>2</sub> target was dissolved in hot aqua regia [24]. Two subsequent additions of HCl and H<sub>2</sub>O<sub>2</sub> served a dual purpose. First, they successfully distilled the germanium target material as [ $^{72}\text{Ge}$ ]GeCl<sub>4</sub>, while keeping the radioarsenic in its non-volatile arsenic (V) oxidation state. Anion exchange chromatography effectively isolated the  $^{72}\text{As}$  from trace germanium target material and  $^{67}\text{Ga}$ .

The separation of  $^{76}\text{As}$  from the  $^{76}\text{Ge}$  target material can be carried out in a similar way to the separation of  $^{72}\text{As}$ .

### 4.5. ASTATINE-211

Vaidyanathan and Zalutsky [28] reported on the targeted radiotherapy alpha emitters, including  $^{213}\text{Bi}$ ,  $^{211}\text{At}$ ,  $^{223}\text{Ra}$  and  $^{225}\text{Ac}$ , and noted that although each has its pros and cons, the decay properties, half-life and chemistry of  $^{211}\text{At}$  perhaps allow higher versatility of applications (Table 6). Applications for  $^{211}\text{At}$  described by Vaidyanathan and Zalutsky include, but are not limited to, [ $^{211}\text{At}$ ]At-astatide (e.g. for thyroid cancer) and  $^{211}\text{At}$ -MABG (meta-astatobenzylguanidine) as an analogue to metaiodobenzylguanidine (MIBG) for neuroendocrine tumour therapy, as well as various  $^{211}\text{At}$ -peptides, antibodies and antibody fragments with applications in colon cancer, ovarian cancer, thyroid cancer, etc. Selected clinical trials using  $^{211}\text{At}$  are also currently reported.<sup>5</sup>

<sup>5</sup> Available at <https://clinicaltrials.gov>

Further elaborating on the decay of  $^{211}\text{At}$ , upon alpha decay (41.80%) to  $^{207}\text{Bi}$ ,  $^{207}\text{Bi}$  is itself radioactive with a half-life of 31.55 y and decays by electron capture (EC) ( $\approx 100\%$ ) to stable  $^{207}\text{Pb}$ . For EC decay (58.20%) to  $^{211}\text{Po}$ , the  $^{211}\text{Po}$  has a half-life of 516 ms and alpha decays (100%) to stable  $^{207}\text{Pb}$ . It needs additionally to be noted that although the gamma ray intensity of  $^{211}\text{At}$  is very low, there are numerous X rays with energies  $>70$  keV (i.e.  $>40\%$ ).

TABLE 6. PROPERTIES OF ASTATINE-211 [1, 29]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
At-211	7.214 h	$\alpha$ (41.80%) EC (58.20%)	687.0 keV (0.261%)	$^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$

#### 4.5.1. Production parameters

While more exotic routes have been described in the literature, the dominant route for  $^{211}\text{At}$  production is via  $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$  ( $E_{\text{th}} = 20.718$  MeV), described by Zalutsky et al. [30]. There are more than 30 cyclotrons globally that are suitable for  $^{211}\text{At}$  production via this scheme. From a target material perspective, there is no need for isotopically enriched materials as bismuth is naturally monoisotopic. The alpha energy needs, however, to be limited to a maximum of  $\sim 28$  MeV to avoid co-production of radiotoxic  $^{210}\text{Po}$  ( $T_{1/2} = 138.376$  d) by the  $^{209}\text{Bi}(\alpha,3n)^{210}\text{At} \rightarrow ^{210}\text{Pb}$  reaction scheme ( $E_{\text{th}} = 28.613$  MeV).

#### 4.5.2. Targetry and separation chemistry

Bismuth targets for  $^{211}\text{At}$  production have included both internal [30, 31] and external [32, 33] target configurations, with target material being almost exclusively bismuth metal. Due to the low melting point of bismuth metal (271.4°C), it is important that the target is well cooled during irradiation. Methods for bismuth target preparation have included evaporation onto aluminium [31], electroplating onto copper [34] and melting of bismuth onto aluminium [32–34]. Subsequent milling of the bismuth layer is suggested prior to irradiation to improve uniformity. Previous methods have all successfully been used for  $^{211}\text{At}$  production. However, challenges may be noted for copper from a radiation handling perspective due to potential co-production of  $^{66}\text{Ga}$  and  $^{68}\text{Ga}$ .

For isolating the  $^{211}\text{At}$  from the bismuth target, Zalutsky provides a detailed review of the two main strategies [29] (i.e. both dry distillation in a quartz vessel and wet chemistry):

- For dry distillation in a quartz vessel, which is more common than wet chemical processing, typical parameters may include treating at temperatures of 650–800°C for 30 min under nitrogen or argon atmosphere. Numerous methods for trapping the volatile  $^{211}\text{At}$  are described.
- Wet chemistry methods have largely been based on liquid–liquid extraction (i.e. target dissolution with acid and extraction of the  $^{211}\text{At}$  into an organic solvent such as butyl or isopropyl ether). However, recent efforts [35] have explored a polyethylene glycol (PEG) based solid phase extraction approach. Recent efforts on automating the wet chemical processing of  $^{211}\text{At}$  are reported by O’Hara et al. [36, 37].

Although radiopharmaceutical labelling with  $^{211}\text{At}$  is not discussed herein, it needs to be highlighted that there are no stable isotopes of astatine and the longest lived isotope of astatine (i.e.  $^{210}\text{At}$ ) has a half-life of only 8.1 h. Consequently, there may be additional challenges in developing labelling methods

as the use of stable or long lived astatine isotopes is not possible. Two recent literature reviews focusing on radiolabelling with  $^{211}\text{At}$  are found in Refs [38, 39].

#### 4.6. BISMUTH-213

The potential of targeted therapy with the alpha emitter  $^{213}\text{Bi}$  has been demonstrated in several preclinical and clinical studies. The results have provided evidence for its therapeutic efficacy. Methods for the production of  $^{225}\text{Ac}$  and  $^{225}\text{Ac}/^{213}\text{Bi}$  radionuclide generators were reviewed in 2011 [40]. However, in the past few years, phase I clinical trials have demonstrated the therapeutic potential of the bismuth radioisotope,  $^{213}\text{Bi}$ , in patients with leukaemia. Bismuth-213, which emits a 6 MeV alpha particle, is delivered to bone marrow, the spleen and blood via the monoclonal antibody conjugate [ $^{213}\text{Bi}$ ]CHX-A-DTPA-HuM195 [41]. Its effectiveness has also been shown in vitro and in humans using an anti-CD33 monoclonal antibody for the treatment of leukaemia. The kinetics and geometry of single-cell killing, however, might not be predictive of killing micrometastatic clusters of expected tumour cells in the early spread of carcinomas. Recently, a prostate-specific, alpha particle emitting agent capable of internalizing into target cells and selectively killing individual cells and spheroid clusters, as well as prolonging tumour free survival and reducing prostate-specific antigen in prostate mouse models, has also been demonstrated. Various new and ongoing human clinical trials are set to treat metastatic prostate cancer worldwide.

TABLE 7. PROPERTIES OF BISMUTH-213 [1, 40]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Bi-213	45.6 min	$\alpha$ (2.1%) $\beta^-$ (97.9%) (see Fig. 9)	440.46 keV	n.a. <sup>a</sup>	Produced from the decay of $^{225}\text{Ac}$

<sup>a</sup> n.a.: not applicable.

##### 4.6.1. Production parameters

The decay modes of  $^{213}\text{Bi}$  are shown in Table 7 and Fig. 9. For the production parameters of  $^{213}\text{Bi}$ , see Section 4.2.1 on  $^{225}\text{Ac}$ .

##### 4.6.2. Targetry and separation chemistry

For optimal use of  $^{213}\text{Bi}$  radiopharmaceuticals derived from the  $^{225}\text{Ac}/^{213}\text{Bi}$  generator, it is essential to minimize the concentrations of the other decay products such as  $^{221}\text{Fr}$ ,  $^{209}\text{Pb}$  and  $^{225}\text{Ac}$  in the final solution [42, 43]. In order to obtain better quality  $^{213}\text{Bi}$  elution, the first 2 mL of the generator eluate can be used to avoid unwanted  $^{221}\text{Fr}$ , as well as obtaining a high specific activity solution for the labelling. Lead-209 can be removed from the final product using a size exclusion purification column due to Pb-CHX-A-DTPA complex instability. In order to reduce the level of  $^{225}\text{Ac}$  generator breakthrough, especially for clinical products, some actions on the column are recommended, including a dilute HCl prewash, application of an external guard-column post-generator and the use of a size exclusion column to isolate the purified radiolabelled compound (in case of antibodies and fragments).

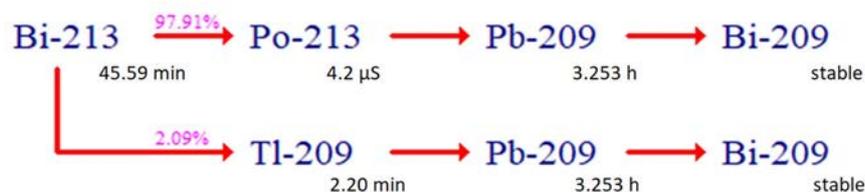


FIG. 9. Decay scheme of  $^{213}\text{Bi}$ .

#### 4.7. BROMINE

Bromine radioisotopes ( $^{75,76g,77g,80m}\text{Br}$ ) are of interest for the creation of alternative radiohalogen analogues of fluorine and iodine compounds and for the development of theranostic radiopharmaceuticals using  $^{75,76g}\text{Br}$  for PET imaging and  $^{77g,80m}\text{Br}$  for therapy. Much of the radiochemistry methodology previously developed for radioiodine is applicable to radiobromine. For these reasons, bromine radioisotopes have been used in many preclinical experiments and several clinical research studies. Radiobromine pharmaceuticals include Br-BFU (bromofluorodeoxyuridine), a potential proliferation marker, Br-MBBG (metabromobenzylguanidine), the bromine analogue of MIBG, as well as several other brominated amino acid analogues [44–46].

TABLE 8. PROPERTIES OF BROMINE [1, 47]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Br-75	97 min	$\beta^+$ (75%) $\beta^+_{\text{mean}} = 730 \text{ keV}$	286 keV (88%)	$^{76}\text{Se}(p,2n)^{75}\text{Br}$ $^{74}\text{Se}(d,n)^{75}\text{Br}$ $^{78}\text{Kr}(d,\alpha n)^{75}\text{Br}$	Decays to radioactive daughter ( $^{75}\text{Se}$ $T_{1/2} = 120 \text{ d}$ )
Br-76g	16.2 h	$\beta^+$ (55%) $\beta^+_{\text{mean}} = 1180 \text{ keV}$	559 keV (74%)	$^{76}\text{Se}(p,n)^{76}\text{Br}$	
Br-77g	57.0 h	EC (98.5%)	234 keV (23%)	$^{77}\text{Se}(p,n)^{77}\text{Br}$ $^{78}\text{Se}(p,2n)^{77}\text{Br}$ $^{76}\text{Se}(d,n)^{77}\text{Br}$ $^{80}\text{Kr}(p,\alpha)^{77}\text{Br}$ $^{78}\text{Kr}(p,2p)^{77}\text{Br}$	
Br-80m	4.42 h	Isomeric transition	37 keV (39%)	$^{80}\text{Se}(p,n)^{80m}\text{Br}$ $^{83}\text{Kr}(p,\alpha)^{80m}\text{Br}$	Decays to radioactive daughter ( $^{80g}\text{Br}$ $\beta^-$ , $T_{1/2} = 17.7 \text{ min}$ )

##### 4.7.1. Production parameters

The desired radioisotopes of bromine can be produced via relatively low energy proton or deuteron irradiation of selenium targets via the  $^{76}\text{Se}(p,2n)^{75}\text{Br}$ ,  $^{74}\text{Se}(d,n)^{75}\text{Br}$ ,  $^{76}\text{Se}(p,n)^{76}\text{Br}$ ,  $^{77}\text{Se}(p,n)^{77}\text{Br}$ ,  $^{78}\text{Se}(p,2n)^{77}\text{Br}$ ,  $^{76}\text{Se}(d,n)^{77}\text{Br}$  and  $^{80}\text{Se}(p,n)^{80m}\text{Br}$  reactions (Table 8). As the natural abundance of many of the selenium target isotopes is low, typically enriched targets are used to maximize yields and minimize impurities. For lower energy cyclotrons, the (p,n) reactions show high cross-sections between 20–8 MeV, whereas for slightly higher energy cyclotrons, the  $^{78}\text{Se}(p,2n)^{77}\text{Br}$  reaction between 25–15 MeV has advantages due to the higher natural abundance of  $^{78}\text{Se}$  [47].

An alternative production route is via the irradiation of krypton targets to produce radiobromine via the  $^{78}\text{Kr}(d,\alpha)^{75}\text{Br}$ ,  $^{80}\text{Kr}(p,\alpha)^{77g}\text{Br}$ ,  $^{78}\text{Kr}(p,2p)^{77g}\text{Br}$  and  $^{83}\text{Kr}(p,\alpha)^{80m}\text{Br}$  reactions [48]. While the yields for the krypton based routes are lower than the selenium reactions, the krypton route may offer the advantage of decreased impurities and more straightforward isolation chemistry.

#### 4.7.2. Targetry and separation chemistry

Elemental selenium has undesirable properties for cyclotron target material with a low melting point (217°C) and high vapour pressure, and is therefore not used directly for the production of radiobromine. Targets may be prepared of refractory selenium compounds, including CoSe, NiSe and Cu<sub>2</sub>Se [44, 49]. These targets must be carefully cooled and can only accommodate modest beam currents to prevent the accidental in situ distillation of the produced radiobromine.

Radiobromine is separated from solid targets via thermal chromatography (often referred to as dry distillation) or thermal diffusion [44, 49, 50]. For thermal chromatography, the target is placed in a high temperature oven (800–1050°C) and the bromine is distilled into a carrier gas flow and isolated downstream. For thermal diffusion, a similar process is followed without a gas flow, upon which radiobromine may be washed from the target surface. Ideally, for such thermal methods, the radiobromine is distilled out of the target material with little impact on the target itself, thus allowing the target material to then be reused for subsequent irradiations. Practically, however, some degradation of the target is noted during this process and thus a single target can only be used a limited number of times.

The recovery of radiobromine from krypton targets follows previous reported examples similar to the recovery of radioiodine from xenon gas or radiochlorine from argon targets [51, 52]. The halogen adheres to the walls of the target and the target gas is cryo-trapped to recover for use for future irradiations. The halogens (and impurities) are then rinsed off the target walls [53]. Several rubidium isotopes are co-produced using this route and must be separated using ion exchange.

### 4.8. CALCIUM-47

Calcium-47 may be of interest for use as a parent for the generator production of the therapeutic  $^{47}\text{Sc}$ . While this has been suggested, this concept is in an early stage of technology development. For more details on the application of  $^{47}\text{Sc}$ , please see the recent IAEA publication, IAEA-TECDOC-1945 [54] or Section 4.23 of this publication.

TABLE 9. PROPERTIES OF CALCIUM-47 [55]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Ca-47	4.54 d	$\beta^-$ (100%) $\beta^-_{\text{mean}} = 400 \text{ keV}$	1297 keV (67%)	$^{48}\text{Ca}(p,pn)^{47}\text{Ca}$	Generator for $^{47}\text{Sc}^a$

<sup>a</sup> See also Table 24.

#### 4.8.1. Production parameters

The production of  $^{47}\text{Ca}$  can be achieved via irradiation of calcium targets (Table 9) [55]. This production route results in a product with low specific activity. However, as this isotope is of interest as a generator for  $^{47}\text{Sc}$ , which can be separated in high specific activity from the target material, this may not be a concern.

#### 4.8.2. Targetry and separation chemistry

Targets may be prepared from elemental calcium, calcium carbonate or calcium oxide. If enriched  $^{48}\text{Ca}$  is used, the target material may be dissolved and incorporated into a generator after irradiation without additional purification.

#### 4.9. COBALT

Cobalt-55 and  $^{58\text{m}}\text{Co}$  are of interest for the creation of theranostic radiopharmaceuticals using  $^{55}\text{Co}$  for PET imaging and  $^{58\text{m}}\text{Co}$  for therapy. In particular, the chemistry and biochemistry of cobalt can enable the formation of complexes that may be more stable in vivo than some of the analogues prepared with radiocopper [56–58]. Additionally, the biochemistry of cobalt as an ion has been employed for PET imaging of stroke and other disease states using [ $^{55}\text{Co}$ ]CoCl<sub>2</sub> in humans [59–61].

TABLE 10. PROPERTIES OF COBALT [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Co-55	17.53 h	$\beta^+$ (76%) $\beta^+$ <sub>mean</sub> = 570 keV	931 keV (75%)	$^{58}\text{Ni}(p,\alpha)^{55}\text{Co}$ $^{54}\text{Fe}(d,n)^{55}\text{Co}$	Decays to $^{55}\text{Fe}$ ( $T_{1/2} = 2.75$ y)
Co-58m	9.10 h	Isomeric transition (100%)	24.9 keV (0.04%)	$^{58}\text{Fe}(p,n)^{58\text{m}}\text{Co}$ $^{57}\text{Fe}(d,n)^{58\text{m}}\text{Co}$	Decays to $^{58\text{g}}\text{Co}$ ( $T_{1/2} = 70.88$ d)

##### 4.9.1. Production parameters

Production of  $^{55}\text{Co}$  is typically via proton irradiation of natural or enriched nickel targets [56, 62–66] (Table 10). Although the cross-section for  $^{55}\text{Co}$  increases at higher energies for the  $^{58}\text{Ni}(p,\alpha)^{55}\text{Co}$  reaction, typically targets are irradiated at lower than 15 MeV, since  $^{57}\text{Co}$  is co-produced directly by the  $^{60}\text{Ni}(p,\alpha)^{57}\text{Co}$  reaction when using nickel targets of natural composition. Also,  $^{57}\text{Co}$  can be produced from the decay of  $^{57}\text{Ni}$ , which is produced via the  $^{58}\text{Ni}(p,pn)^{57}\text{Ni}$  reaction.

The production of  $^{55}\text{Co}$  via the  $^{54}\text{Fe}(d,n)^{55}\text{Co}$  reaction using electroplated enriched iron targets has also been reported [63]. This route has a higher cross-section than the proton route and is to be considered if deuterons are available, particularly if there is interest in  $^{58\text{m}}\text{Co}$ , as the same targetry and chemistry can be used for both isotopes if using iron targets.

For the production of  $^{58\text{m}}\text{Co}$ , both  $^{58}\text{Fe}(p,n)^{58\text{m}}\text{Co}$  and  $^{57}\text{Fe}(d,n)^{58\text{m}}\text{Co}$  routes can be used, with the deuteron reaction having the advantage of a lower cost target material and the proton production route having a higher cross-section. When using the proton route, care needs to be taken to limit the proton energy (<12 MeV) to avoid production of the long lived cobalt impurity via the  $^{58}\text{Fe}(p,2n)^{57}\text{Co}$  reaction.

##### 4.9.2. Targetry and separation chemistry

Enriched electroplated nickel targets can be prepared using well developed chemistry for the electroplating of  $^{64}\text{Ni}$  for the production of  $^{64}\text{Cu}$  [56, 66]. Following irradiation of the target,  $^{55}\text{Co}$  can be separated from the nickel target material by anion exchange chromatography. The separation of the target material is ideally conducted shortly after the irradiation before significant decay of the co-produced  $^{57}\text{Ni}$  (which can be chemically separated from  $^{55}\text{Co}$ ) to  $^{57}\text{Co}$  (which cannot be chemically separated from  $^{55}\text{Co}$ ).

Iron targets can be electroplated using established techniques [67]. After the irradiation, the target is dissolved for purification via ion exchange. For the separation of radiocobalt from iron, anion exchange chromatography can be used [67]. In another recent work, a branched diglycolamide resin was employed for the purification of  $^{55}\text{Co}$  from iron targets, resulting in a high purity product in a small volume [63].

As with the production of many radiometals, particularly those of transition metal elements, care must be taken to avoid the introduction of cold metal contaminants by using high purity reagents in order to yield a product with high specific activity.

#### 4.10. COPPER

Copper radioisotopes have proven to be useful in both clinical and preclinical studies, as a well established coordination chemistry [68] leads to facile labelling of a wide variety of molecules.

Copper radioisotopes such as  $^{60}\text{Cu}$ ,  $^{61}\text{Cu}$ ,  $^{62}\text{Cu}$  and  $^{64}\text{Cu}$  have been used in PET imaging [69, 70], while  $^{64}\text{Cu}$  and  $^{67}\text{Cu}$  can be used for in vivo targeted radiation therapy. Pairs of copper isotopes, selected considering decay properties and the application/kinetics in question, can thus be used in a theranostic pairing approach [71,72]. It needs to be noted that the US Food and Drug Administration approved the first  $^{64}\text{Cu}$  labelled tracer in 2020. With ongoing interest in copper radioisotopes, production and purification of copper isotopes has been reported extensively in several IAEA documents including for  $^{61}\text{Cu}$  [73], for  $^{64}\text{Cu}$  [66], and for  $^{67}\text{Cu}$  [54].

Considering the copper labelled molecules, diacetyl-bis (4-methylthiosemicarbazonato) (ATSM) is prevalent in the literature as a hypoxia marker [74, 75], but a wide variety of compounds, including antibodies and peptides for tumour targeting, peptides for tumour angiogenesis, somatostatin analogues for targeting neuroendocrine tumours, prostate-specific membrane antigen (PSMA) for prostate cancer and biomarkers for Wilson's disease or myocardial perfusion, have been studied and extensively reported [76–80]. Considering the labelling strategy, the use of the 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) chelator is still common, though 1,4,7-triazacyclononane- $\text{N,N',N''}$ -triacetic acid (NOTA) and other newer chelators are gaining traction, as these have been shown to be more stable in vivo [81] and may offer room temperature labelling conditions.

TABLE 11. PROPERTIES OF COPPER [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Cu-60	23.7 min	$\beta^+$ (93%) $\beta^+_{\text{mean}} = 970 \text{ keV}$	872 keV (49%)	
Cu-61	3.35 h	$\beta^+$ (61%) $\beta^+_{\text{mean}} = 500 \text{ keV}$	532.8 keV (51%)	$^{61}\text{Ni}(\text{p,n})^{61}\text{Cu}$ $^{60}\text{Ni}(\text{d,n})^{61}\text{Cu}$ $^{64}\text{Zn}(\text{p},\alpha)^{61}\text{Cu}$
Cu-64	12.7 h	$\beta^-$ (38.5%) $\beta^-_{\text{mean}} = 191 \text{ keV}$ $\beta^+$ (17.60%) $\beta^+_{\text{mean}} = 278 \text{ keV}$	190.7 keV (38.5%) 278 keV (19.7%)	$^{64}\text{Ni}(\text{p,n})^{64}\text{Cu}$
Cu-67	2.6 d	$\beta^-$ (100%) $\beta^-_{\text{mean}} = 141 \text{ keV}$	121 keV (57%)	$^{70}\text{Zn}(\text{p},\alpha)^{67}\text{Cu}$ $^{64}\text{Ni}(\alpha,\text{p})^{67}\text{Cu}$

#### 4.10.1. Production parameters

The main production schemes for the copper radioisotopes, as shown in Table 11, employ either enriched nickel or zinc targets. In particular, when using the  $^{64}\text{Ni}(p,n)^{64}\text{Cu}$  reaction, enriched  $^{64}\text{Ni}$  is used to avoid the co-production of long lived cobalt radioisotopes. Traditionally, solid targets are used for large scale production.

#### 4.10.2. Targetry and separation chemistry

The preparation of these targets (typically using electroplating on inert backings) is well developed, as is the separation chemistry (typically through ion exchange). Details on target preparation, dissolution, separation chemistry and enriched material recovery are reported in Ref. [1] for both nickel and zinc solid targets. Production of  $^{64}\text{Cu}$  has been extensively addressed in Refs [54, 66, 82, 83], with recent cassette-based automated purification of  $^{61}\text{Cu}$  and  $^{64}\text{Cu}$  from solid targets reported in Ref. [84]. A literature review on the production, separation and use of  $^{67}\text{Cu}$  is also available [85].

Specific resins are commercially available for the separation chemistry of produced copper isotopes, although these require sensitive pH adjustment and thus may pose challenges for solid target production.

Recent efforts have investigated the production of copper isotopes using liquid targets, namely for  $^{61}\text{Cu}$  production from  $^{\text{nat}}\text{Zn}$  or  $^{64}\text{Zn}$  [86] and for  $^{64}\text{Cu}$  production from  $^{64}\text{Ni}$  [87]. Significant benefits in both purification and labelling time are reported, eliminating the pre- and post-irradiation target preparation and handling issues typically characterizing solid target methodologies. Reported yields and reliability, together with complete automation [88], foresee liquid targets as a suitable complementary approach for low scale production of  $^{61}\text{Cu}$  for human use, although solid targets are likely to be necessary for widespread distribution of  $^{64}\text{Cu}$ .

One of the main challenges that a site will face in producing copper radioisotopes is the ability to produce adequately high specific activity for receptor targeting applications [89]. Such a task involves great care and know-how (e.g. use of the highest purity, metal-free acids and buffers, additional treatment of reagents, acid washing of all glassware, etc.). Typically, larger scale production of copper radioisotopes will result in a higher quality product.

#### 4.11. ERBIUM-165

Erbium-165 decays by EC without any accompanying gamma radiation, hence it is an ideal candidate for Auger electron therapy. Erbium is a lanthanide element, meaning that it can easily create rather stable complexes (in vitro and in vivo) with commercially available chelators such as DOTA and, similar to radio-yttrium, it can be used for the labelling of monoclonal antibodies and peptides [90]. The only drawback is that it is not possible to use any imaging technique for the follow-up of the biodistribution of radiopharmaceuticals labelled with this radionuclide, since it does not emit radiation that can be detected with imaging techniques commonly used in nuclear medicine.

TABLE 12. PROPERTIES OF ERBIUM-165 [91]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Er-165	10.36 h	EC (100%)	n.a. <sup>a</sup>	$^{165}\text{Ho}(p,n)^{165}\text{Er}$ $^{165}\text{Ho}(d,2n)^{165}\text{Er}$ $^{\text{nat}}\text{Er}(p,xn)^{165}\text{Tm} \rightarrow ^{165}\text{Er}$ $^{166}\text{Er}(p,2n)^{165}\text{Tm} \rightarrow ^{165}\text{Er}$

<sup>a</sup> n.a.: not applicable.

#### 4.11.1. Production parameters

The easiest way to produce  $^{165}\text{Er}$  is via the  $^{165}\text{Ho}(p,n)^{165}\text{Er}$  and  $^{165}\text{Ho}(d,2n)^{165}\text{Er}$  nuclear reactions (Table 12) for which the energy of projectiles can be relatively low. Since holmium is a monoisotopic element, the target material is relatively inexpensive and no recovery is required. The practical energy range for the (p,n) production route is 12→7 MeV and for the (d,2n) routes is 16→11 MeV [92]. In both cases  $^{166}\text{Ho}$  ( $T_{1/2} = 26.824$  h,  $\beta^-$ , 100%) as a radionuclidic impurity has been experimentally identified, with the (p,n) production path leading to a purer product [91].

The  $^{nat}\text{Er}(p,xn)^{165}\text{Tm} \rightarrow ^{165}\text{Er}$  production path is only feasible at relatively high energies of protons (in the 70→18 MeV energy range) and the production process is much more complicated, as a two step separation process is required to ensure high specific activity of  $^{165}\text{Er}$  [93]. The highest radionuclidic purity that can be achieved is in the 29→20 MeV energy range [91].

The  $^{166}\text{Er}(p,2n)^{165}\text{Tm} \rightarrow ^{165}\text{Er}$  reaction is feasible for medium energy cyclotrons, since the practical energy range for this reaction is 23→16 MeV on an oxide target [94].

#### 4.11.2. Targetry, irradiation parameters and separation chemistry

It is not possible to deposit lanthanides onto appropriate target backings by electrodeposition; thus, irradiation of metal foils or compacted powder tablets of oxides of holmium or erbium are the only options for  $^{165}\text{Er}$  production. The thermal conductivity of erbium and holmium is 14.5 and 16.2  $\text{W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ , respectively [95], which is relatively low, and the thermal conductivity of compacted oxide powders is even lower. Thus, high beam current acceptance of these targets, which limits the production rates of  $^{165}\text{Er}$ , cannot be expected. Dedicated target stations suitable for irradiation of thin foils or compacted powders are required for this purpose.

Chemical separation of lanthanides is one of the most challenging separation processes due to the fact that all lanthanides are chemically very similar. Ion exchange chromatographic column separation using Aminex A5 resin in  $\text{NH}_4^+$ -form (Bio-Rad) and various concentrations of  $\alpha$ -hydroxyisobutyric acid (2-hydroxy-2-methylpropionic acid) at pH5 is known to be suitable for the separation of lanthanides [96], and a simulated process has been reported to be suitable for the separation of bulk amounts of holmium from trace amounts of  $^{165}\text{Er}$  [90]. Recent efforts reported in Ref. [97] include proton irradiation of pressed  $^{nat}\text{Ho}_2\text{O}_3$  targets followed by a two-column purification process to isolate  $^{165}\text{ErCl}_3$ .

Alternatively, the separation of  $^{165}\text{Er}$  from the irradiated foil of holmium can be performed by dissolving the holmium foil in nitric acid, loading a chromatographic column (LN2, Triskem) with the solution and gradually eluting the column with different concentrations of nitric acid [91].

### 4.12. GALLIUM

There are several cyclotron produced isotopes of gallium which have applications in PET (i.e.  $^{66}\text{Ga}$  and  $^{68}\text{Ga}$ ) and single photon imaging (i.e.  $^{67}\text{Ga}$ ). Of these,  $^{67}\text{Ga}$  and  $^{68}\text{Ga}$  are in routine clinical use;  $^{67}\text{Ga}$  is most commonly used as [ $^{67}\text{Ga}$ ]Ga-citrate for imaging of inflammation and infection. For  $^{68}\text{Ga}$ , many areas are under research investigation. However, the two main applications of  $^{68}\text{Ga}$  today are in theranostics: the imaging of neuroendocrine tumours by means of somatostatin receptor targeting agents [98] and the imaging of prostate cancer by PSMA targeting agents [99]. In fact, market authorization with cyclotron based  $^{68}\text{Ga}$  for two such tracers, namely [ $^{68}\text{Ga}$ ]Ga-PSMA-11 and [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC, was granted by the US Food and Drug Administration in 2020. The application of  $^{68}\text{Ga}$  to the imaging of inflammation and infection has also been reported [100–102].

TABLE 13. PROPERTIES OF GALLIUM [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Ga-66	9.49 h	$\beta^+$ (57%) $\beta^+_{\text{mean}} = 1750 \text{ keV}$	1039.220 keV (37.0%)	$^{66}\text{Zn}(p,n)^{66}\text{Ga}$	
Ga-67	3.2617 d	EC (100%)	93.310 keV (38.81%)	$^{67}\text{Zn}(p,n)^{67}\text{Ga}$ $^{66}\text{Zn}(d,n)^{67}\text{Ga}$	
Ga-68	67.71 min	$\beta^+$ (88.91%) $\beta^+_{\text{mean}} = 829.5 \text{ keV}$	1077.34 keV (3.22%)	$^{68}\text{Zn}(p,n)^{68}\text{Ga}$	Also available from a $^{68}\text{Ge}$ generator <sup>a</sup>

<sup>a</sup> See also Table 14.

#### 4.12.1. Production parameters

Gallium-66 is typically produced from the  $^{66}\text{Zn}(p,n)^{66}\text{Ga}$  reaction ( $E_{\text{th}} = 6.048 \text{ MeV}$ ), whereby irradiation of natural zinc may be used for initial chemistry research/development purposes. Production of  $^{66}\text{Ga}$  by alpha particle irradiation of natural copper has also been reported [103]. Production of  $^{67}\text{Ga}$  can be achieved by proton or deuteron bombardment, through  $^{68}\text{Zn}(p,2n)^{67}\text{Ga}$  ( $E_{\text{th}} = 12.159 \text{ MeV}$ ),  $^{67}\text{Zn}(p,n)^{67}\text{Ga}$  ( $E_{\text{th}} = 1.810 \text{ MeV}$ ) or  $^{66}\text{Zn}(d,n)^{67}\text{Ga}$  ( $E_{\text{th}} = 0 \text{ MeV}$ ) nuclear reactions (Table 13). In the (p,n) and (d,n) reactions, caution in energy selection is required to limit the co-production of  $^{66}\text{Ga}$  ( $T_{1/2} = 9.49 \text{ h}$ ) via the  $^{67}\text{Zn}(p,2n)^{66}\text{Ga}$  ( $E_{\text{th}} = 13.205 \text{ MeV}$ ) or  $^{66}\text{Zn}(d,2n)^{66}\text{Ga}$  ( $E_{\text{th}} = 8.431 \text{ MeV}$ ) reactions.

$^{68}\text{Ge}/^{68}\text{Ga}$  generators are currently the most common method for obtaining  $^{68}\text{Ga}$  (see Section 4.13). However, the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator has the challenges of cost, overall radioactivity and availability. As an alternative to  $^{68}\text{Ge}/^{68}\text{Ga}$  generators, direct production of  $^{68}\text{Ga}$  is possible, the most convenient route being  $^{68}\text{Zn}(p,n)^{68}\text{Ga}$  ( $E_{\text{th}} = 3.758 \text{ MeV}$ ) [104]. Isotopically enriched  $^{68}\text{Zn}$  is required, whereby the maximum energy needs to be limited to minimize co-production of  $^{67}\text{Ga}$  by the  $^{68}\text{Zn}(p,2n)^{67}\text{Ga}$  ( $E_{\text{th}} = 12.159 \text{ MeV}$ ) reaction. A recent IAEA publication, IAEA-TECDOC-1863 [105], addresses the cyclotron based production of  $^{68}\text{Ga}$ .

#### 4.12.2. Targetry and separation chemistry

The traditional method of gallium production is via the irradiation of a solid target of isotopically enriched zinc. Solid zinc target preparation techniques are detailed in Ref. [1] as well as in Ref. [105] on  $^{68}\text{Ga}$  production. Electroplating is the most common technique, using copper [106], silver [107] or platinum [102] backings. However, foil [108] and fused zinc targets [109] have also been reported. The target must be dissolved (typically via HCl) prior to chemical processing.

Production of  $^{68}\text{Ga}$  from liquid targets, using  $^{68}\text{Zn}$  dissolved in nitric acid as the target material [87, 110], has recently been established as a consistent production path with routine clinical implementation demonstrated [111]. Significant benefits in both purification and labelling time are reported, eliminating the need for pre- and post-irradiation solid target preparation and handling. Reported yields and reliability, together with complete automation [111], render liquid targets a suitable alternative approach for  $^{68}\text{Ga}$  production.

Concerning post-irradiation separation of gallium from zinc, solid phase separation is often preferred as it is amenable to radiochemistry automation, examples of which include the use of either cation exchange resin or hydroxamate resin [110]. Numerous other separation schemes have, however, been reported, e.g. thermal diffusion [112], solvent extraction [113, 114] and precipitation [115].

Considering the clinical use of cyclotron based gallium isotopes, a European Pharmacopoeia monograph was published for cyclotron produced [ $^{68}\text{Ga}$ ]GaCl<sub>3</sub> [111]. Clinical implementation of cyclotron based [ $^{68}\text{Ga}$ ]Ga-PSMA-11 has also recently been demonstrated [116].

#### 4.13. GERMANIUM-68

Due to its long half-life,  $^{68}\text{Ge}$  was initially used as a calibration source for PET cameras for attenuation correction. However, the widespread use of PET–CT scanners nowadays has eliminated the need for this application. On the other hand, the ever growing demand for  $^{68}\text{Ga}$ , which can be readily made available using  $^{68}\text{Ge}/^{68}\text{Ga}$  generators, requires mass production of this radioisotope [111]. The  $^{68}\text{Ge}/^{68}\text{Ga}$  generator can typically be used for one year and is an excellent source of positron emitting radioisotopes, which can be used for the on-site synthesis of radiopharmaceuticals for PET imaging, even if the PET centre does not have a nearby cyclotron suitable for radionuclide production. For more details on the applications of  $^{68}\text{Ga}$ , see Section 4.12. There are only a few commercial centres producing this radioisotope, but the ever growing demand for  $^{68}\text{Ge}/^{68}\text{Ga}$  generators is encouraging the establishment of new  $^{68}\text{Ge}$  production centres.

TABLE 14. PROPERTIES OF GERMANIUM-68 [117]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Ge-68	270.9 d	EC (100%)	n.a. <sup>a</sup>	$^{69}\text{Ga}(p,2n)^{68}\text{Ge}$ $^{69}\text{Ga}(d,3n)^{68}\text{Ge}$ $^{\text{nat}}\text{Ga}(p,xn)^{68}\text{Ge}$	$^{68}\text{Ge}$ is used as the parent radioisotope to prepare $^{68}\text{Ga}$ in the form of a $^{68}\text{Ge}/^{68}\text{Ga}$ generator

<sup>a</sup> n.a.: not applicable.

##### 4.13.1. Production parameters

Even though higher yields can be obtained if enriched  $^{69}\text{Ga}$  is used for  $^{68}\text{Ge}$  production, the use of natural gallium is preferred due to the high price of the enriched gallium isotope target material and the complicated chemical procedure for its recycling. High energy deuterons required for the  $^{69}\text{Ga}(d,3n)^{68}\text{Ge}$  reaction at sufficiently high currents are not available, so this production route is not practised for commercial production (Table 14). The practical yield of the  $^{\text{nat}}\text{Ga}(p,xn)^{68}\text{Ge}$  reaction is 1.5 MBq· $\mu\text{A}^{-1}\cdot\text{h}^{-1}$  at 30 MeV [117].

##### 4.13.2. Targetry and separation chemistry

Traditionally, encapsulated metallic gallium or Ga<sub>2</sub>O targets are used for  $^{68}\text{Ga}$  production [118, 119]. Alternatively, gallium-nickel alloys in various proportions (e.g. 70/30 at.%) prepared by electroplating can be used [120]. The advantage of the gallium-nickel alloy targets is that encapsulation is not needed, since the melting point of the alloy is very high (typically above 700°C), so target failure due to breakage of the capsules during irradiation is eliminated, and mechanical operations (opening of the capsule) prior to chemical processing of the irradiated targets are not necessary. If a proton energy in the order of ~30 MeV is the maximum available, plated targets are the only practical route, as higher energy protons are needed to penetrate through the housing of an encapsulated target. Very high beam currents (well above 100  $\mu\text{A}$

on target) and very long irradiation times (typically one month) are needed to obtain reasonable yields of  $^{68}\text{Ge}$ . Before the chemical processing, the irradiated target is typically left for about two weeks for the decay of co-produced short lived radionuclides, among which the most critical is  $^{69}\text{Ge}$  ( $T_{1/2} = 39.05$  h).

Chemical processing of the irradiated targets starts with dissolution in 12M  $\text{H}_2\text{SO}_4$  or 9.0–9.5M HCl, followed by liquid–liquid extraction of  $^{68}\text{Ge}$  using  $\text{CCl}_4$ . Afterwards,  $^{68}\text{Ge}$  is back-extracted into 0.05M HCl and evaporated to the appropriate volume [121, 122]. Alternatively, an ion exchange chromatographic process consisting of several stages can be utilized for the separation and purification of  $^{68}\text{Ge}$  [119]. Recently, a simplified column chromatographic process has been reported, which is very promising, since it is based on a single stage purification process based on a diglycolamide resin (TrisKem International); the process is fast, simple and easy to automate [123].

#### 4.14. INDIUM

Indium-111 is widely used in nuclear medicine for various applications including, but not limited to, labelling of cellular blood components, monoclonal antibodies, myocardial damage detections, abscess localization in polycystic kidneys, radiolabelled immunoglobulin therapies, imaging for cancer, etc. Perhaps the most common application of  $^{111}\text{In}$  is for somatostatin receptor imaging (e.g. octreotide), for  $^{90}\text{Y}/^{177}\text{Lu}$  somatostatin receptor based therapy planning, as well as for imaging of infections through white blood cell labelling. However, the spatial resolution of planar scintigraphy and SPECT does not allow for imaging small tumours and the quantification accuracy, which is critical for radionuclide based therapy, is limited for both methods. Thus, for quantitative and high resolution imaging using the same ligands, the positron emitting  $^{110\text{m}}\text{In}$  is a promising alternative [124].

TABLE 15. PROPERTIES OF INDIUM [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
In-110m	69.1 min	$\beta^+$ (61.3%) $\beta^+_{\text{mean}} = 1011$ keV EC (38%)	657.75 keV (97.74%)	$^{110}\text{Cd}(p,n)^{110\text{m}}\text{In}$
In-111	2.8047 d	EC (100%)	245.35 keV (94.1%)	$^{111}\text{Cd}(p,n)^{111}\text{In}$ $^{112}\text{Cd}(p,2n)^{111}\text{In}$

##### 4.14.1. Production parameters

Indium-110m can be produced by relatively low energy protons through the  $^{110}\text{Cd}(p,n)^{110\text{m}}\text{In}$  nuclear reaction (Table 15). Unfortunately, the higher the energy of the protons, the more  $^{110\text{g}}\text{In}$  ( $T_{1/2} = 4.92$  h) will be co-produced. Indium-110g decays by EC (99.992%), so it does not interfere with the PET imaging. However, the presence of this radionuclide increases the dose delivered to the patient. The only way to get pure  $^{110\text{m}}\text{In}$  is through the  $^{110}\text{Sn}/^{110\text{m}}\text{In}$  generator [125].

Indium-111 can be produced by compact medical cyclotrons through the  $^{111}\text{Cd}(p,n)^{111}\text{In}$  nuclear reaction, but a significantly higher yield can be obtained through the  $^{112}\text{Cd}(p,2n)^{111}\text{In}$  nuclear reaction using 24–30 MeV protons [126, 127].

#### 4.14.2. Targetry and separation chemistry

Cadmium targets for radioindium production are commonly prepared by electroplating thin layers of cadmium over a copper substrate [3]. There are various possibilities for chemical separation of indium from the target matrix, among which the most common starts with dissolving the target in diluted nitric acid containing  $\text{Fe}^{3+}$  as an etching agent, in order to reduce contamination with copper. Next, indium and iron are precipitated by  $\text{NH}_4\text{OH}$  (indium being co-precipitated), allowing for the separation of the dissolved target material (enriched cadmium). The indium containing precipitate is dissolved in 6M HBr, and indium and iron are extracted by di-isopropyl ether, while traces of copper and zinc remain in the aqueous phase. Finally, indium is back-extracted into 7.7M HCl solution, while iron remains in the organic phase. Deep purification of indium (eliminating traces of cadmium) is achieved by column chromatography using DOWEX 1X8, by which the acidity of the product is reduced since 0.05M HCl is used to elute indium [126].

The enriched cadmium is recovered using controlled cathode potential electrolysis, by which traces of copper are eliminated from the recovered cadmium, which can be used for the preparation of new targets [126].

#### 4.15. IODINE

There are several iodine radioisotopes with decay characteristics suitable for PET (e.g.  $^{121}\text{I}$ ,  $^{124}\text{I}$ ) or single photon imaging ( $^{123}\text{I}$ ), which can be readily produced on a cyclotron. Limited clinical studies with  $^{124}\text{I}$  have been performed, whereas  $^{123}\text{I}$  is in routine clinical practice. Considering the use of reactor based  $^{131}\text{I}$  for therapy, iodine can be considered as an element with true theranostic characteristics.

There are many examples of iodine based radiolabelled compounds, including, but not limited to, MIBG (neuroblastoma and pheochromocytoma imaging and therapy), iodoazomycin arabinoside (IAZA) and iodoazomycin galacopyranoside (IAZG) (hypoxia imaging), 1-(2-Deoxy-beta-D-ribofuranosyl)-2,4-difluoro-5-iodobenzene (dRFIB) and 5- $^{123}\text{I}/^{125}\text{I}$ iodo-2'-deoxyuridine (IUdR) (cell proliferation imaging), 2'-fluoro-2'-deoxy-1-beta-D-arabinofuranosyl-5-iodouracil (FIAU) (for monitoring gene therapy), etc. [128].

A dedicated IAEA report on the cyclotron based production of  $^{64}\text{Cu}$  and  $^{124}\text{I}$  was published in 2016 [66], investigating production routes, target preparation, development of radioiodinated synthons and potential applications of  $^{124}\text{I}$ . For a recent review of  $^{124}\text{I}$  radiochemistry, production processes, labelling methods, and immunPET imaging, see Ref. [129].

TABLE 16. PROPERTIES OF IODINE [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
I-121	2.12 h	$\beta^+$ (10.6%) $\beta^+$ <sub>mean</sub> = 470 keV	12.20 keV (84.3%)	$^{122}\text{Te}(p,2n)^{121}\text{I}$ $^{120}\text{Te}(d,n)^{121}\text{I}$
I-123	13.2235 h	EC (100%)	158.97 keV (83.3%)	$^{123}\text{Te}(p,n)^{123}\text{I}$ $^{124}\text{Xe}(p,2n)^{123}\text{Cs} \rightarrow ^{123}\text{Xe} \rightarrow ^{123}\text{I}$ $^{124}\text{Xe}(p,pn)^{123}\text{Xe} \rightarrow ^{123}\text{I}$
I-124	4.1760 d	$\beta^+$ (22.7%) $\beta^+$ <sub>mean</sub> = 820 keV	602.73 keV (62.9%)	$^{124}\text{Te}(p,n)^{124}\text{I}$ $^{124}\text{Te}(d,2n)^{124}\text{I}$ $^{125}\text{Te}(p,2n)^{124}\text{I}$

#### 4.15.1. Production parameters

Two dominant strategies exist for the cyclotron production of iodine radioisotopes — namely, the irradiation of enriched tellurium or enriched xenon gas (Table 16). Tellurium is recommended for the production of  $^{121}\text{I}$  and  $^{124}\text{I}$ . To a limited extent, tellurium may be used for the production of  $^{123}\text{I}$  via the  $^{123}\text{Te}(p,n)^{123}\text{I}$  ( $E_{\text{th}} = 2.027$  MeV) reaction on cyclotrons with proton energies below  $\sim 20$  MeV. However, the purity of the enriched  $^{123}\text{Te}$  target is critical, as even small amounts of  $^{124}\text{Te}$  in the target material will lead to unwanted  $^{124}\text{I}$  co-production. Hence, at least 99.98% enriched  $^{123}\text{Te}$  is recommended for this production path. The preferred route for  $^{123}\text{I}$  production is via the  $^{124}\text{Xe}(p,2n)^{123}\text{Cs} \rightarrow ^{123}\text{Xe} \rightarrow ^{123}\text{I}$  ( $E_{\text{th}} = 15.596$  MeV) and  $^{124}\text{Xe}(p,pn)^{123}\text{Xe} \rightarrow ^{123}\text{I}$  ( $E_{\text{th}} = 10.569$  MeV) pathway with proton energies of  $\sim 30$  MeV.

In the context of  $^{121}\text{I}$  production, the  $^{122}\text{Te}(p,2n)^{121}\text{I}$  ( $E_{\text{th}} = 13.023$  MeV) reaction is preferred over the  $^{120}\text{Te}(d,n)^{121}\text{I}$  ( $E_{\text{th}} = 0$  MeV) reaction, given the significantly higher natural isotopic abundance of  $^{122}\text{Te}$  (i.e. 2.55%) compared with  $^{120}\text{Te}$  (i.e. 0.09%). Caution is warranted for irradiation above  $\sim 24$  MeV to limit the  $^{122}\text{Te}(p,3n)^{120\text{m}}\text{I}$  ( $T_{1/2} = 53$  m) and  $^{120\text{g}}\text{I}$  ( $T_{1/2} = 81.6$  m) reactions ( $E_{\text{th}} = 23.680$  MeV).

The  $^{124}\text{Te}(p,n)^{124}\text{I}$  ( $E_{\text{th}} = 3.973$  MeV) reaction is the most common route to  $^{124}\text{I}$  production, although the proton energy needs to be limited to  $\sim 12$  MeV to minimize the co-production of  $^{123}\text{I}$  via the  $^{124}\text{Te}(p,2n)^{123}\text{I}$  reaction ( $E_{\text{th}} = 11.528$  MeV), or if higher energy is used, sufficient time needs to be allowed for the decay of co-produced  $^{123}\text{I}$ . For the production of  $^{124}\text{I}$ , both the  $^{124}\text{Te}(d,2n)^{124}\text{I}$  ( $E_{\text{th}} = 6.266$  MeV) and  $^{125}\text{Te}(p,2n)^{124}\text{I}$  ( $E_{\text{th}} = 10.595$  MeV) reactions will also produce  $^{124}\text{I}$  in high yield. However, caution is required with these reactions due to the co-production of  $^{125}\text{I}$ . Numerous additional, less common routes to  $^{124}\text{I}$  production are possible [128], including the use of antimony targets.

#### 4.15.2. Targetry and separation chemistry

##### 4.15.2.1. Tellurium targets

Tellurium targets have been described elsewhere extensively [9, 66]. While electroplated tellurium targets followed by wet chemical processing to extract the iodine have been reported [130], in general, the primary production and separation scheme for tellurium based iodine production includes irradiation of a melted  $\text{TeO}_2$  target (often with up to 6%  $\text{Al}_2\text{O}_3$ ), upon which the radioiodine is recovered by thermal chromatography [131, 132]. While the use of  $\text{TeO}_2$  targets offers the benefit of re-irradiating the same target, such targets are limited to irradiation currents of typically less than 30  $\mu\text{A}$  and often less than 10  $\mu\text{A}$ .

##### 4.15.2.2. Xenon targets

To maximize production of  $^{123}\text{I}$ , when higher energy (e.g.  $\sim 30$  MeV) protons are available, the preferred route for  $^{123}\text{I}$  production is via the  $^{124}\text{Xe}(p,2n)^{123}\text{Cs} \rightarrow ^{123}\text{Xe} \rightarrow ^{123}\text{I}$  and  $^{124}\text{Xe}(p,pn)^{123}\text{Xe} \rightarrow ^{123}\text{I}$  reactions. In this scheme, following bombardment of the enriched xenon gas, the irradiated gas is left to sit in either the target or a holding vessel for decay. Next, the enriched xenon gas is cryogenically recovered, upon which the target or holding vessel is rinsed to recover the  $^{123}\text{I}$ . As the natural abundance of  $^{124}\text{Xe}$  is 0.0952%, the target gas is quite expensive and thus great care needs to be taken to avoid leaks or loss of the target material.

#### 4.16. IRON-52

The half-life of  $^{52}\text{Fe}$  (8.275 h) allows the study of kinetics up to 24 h after injection, and it has been used to study the transfer of iron into various organs, especially the heart (for blood kinetics), liver and bone marrow using PET imaging with an axial field of view of 10 cm [133]. By compensating for the interfering radioactive daughter  $^{52\text{m}}\text{Mn}$  activity, the actual  $^{52}\text{Fe}$  contribution to the PET images could be determined. In one study, using  $^{52}\text{Fe}$ , rate constants were estimated for iron transfer from the blood to a

pool of iron. Iron-52 has also been used to study whether iron uptake in brain tumours is associated with their histological grade [134]. It was concluded that  $^{52}\text{Fe}$  accumulation in tumours is governed by tracer uptake at the blood–brain barrier and does not reflect the number of transferrin receptors at the level of tumour cells.

TABLE 17. PROPERTIES OF IRON-52 [128]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Fe-52	8.275 h	$\beta^+$ (55%) EC (45%)	168.688 keV (4.35%)	$^{50}\text{Cr}(\alpha,2n)^{52}\text{Fe}$

#### 4.16.1. Production parameters

The target is typically elemental chromium either as a powder or electroplated onto appropriate backing. This radionuclide with  $T_{1/2} = 8.275$  h could be identified with reasonable certainty by the intense  $\gamma$ -line at 168.688 keV (99.2%). The metastable state with 45.9 s half-life decays for 99.58% by  $\beta^+$  to the ground state of  $^{52}\text{Mn}$ . The excitation curve of the  $^{50}\text{Cr}(\alpha,2n)^{52}\text{Fe}$  reaction has an effective threshold of 18 MeV corresponding to the theoretical one (Table 17). The maximum value of the excitation function is  $\sim 22$  mb at 32 MeV [135]. The shorter lived  $^{53}\text{Fe}$  can be allowed to decay out before processing of the target to ensure the maximum purity of the radioisotope. Other potentially interfering reactions have very low cross-sections and therefore can be ignored.

#### 4.16.2. Targetry and separation chemistry

A method for separating iron from the chromium target has been published before [136–138]. In general, the chromium is dissolved in HCl and then solvent extraction is used to isolate  $^{52}\text{Fe}$  with minimal chromium contamination. By repeated ether extractions and washings with ether-saturated 8M HCl, a suitable separation of iron from Cu, Co, Mn, Ni, Al, Cr, Zn,  $\text{V}^{4+}$  and Ti can be achieved. In the presence of carrier iron, using redistilled di-isopropyl ether and maintaining the 8M HCl concentration, a 99% efficiency of the extraction is affordable.

#### 4.17. MANGANESE-52g

Manganese-52g is a positron emitter with imaging applications in the development of longer lived targeted imaging agents and dual modality PET–MRI agents [139, 140]. Additionally, there is interest in  $^{52g}\text{Mn}$  for the investigation of the biological roles of manganese, including toxicity [141, 142]. This isotope has been used in a number of basic science and preclinical imaging studies [143, 144].

TABLE 18. PROPERTIES OF MANGANESE-52g [145–147]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Mn-52g	5.59 d	$\beta^+$ (29.4%) $\beta^+_{\text{mean}} = 242$ keV	1434 keV (100%)	$^{52}\text{Cr}(p,n)^{52g}\text{Mn}$

#### 4.17.1. Production parameters

Manganese-52g can be produced by proton bombardment of chromium via the  $^{52}\text{Cr}(p,n)^{52}\text{Mn}$  reactions (Table 18). The optimal energy range to maximize the yield is 20→6 MeV. Typically, targets of natural isotope composition are used, although this leads to the co-production of small amounts of the long lived contaminant  $^{54}\text{Mn}$  via the  $^{54}\text{Cr}(p,n)^{54}\text{Mn}$  reaction [145–147]. While  $^{54}\text{Mn}$  production is low (due to the low natural abundance, i.e. 2.4% of  $^{54}\text{Cr}$ ),  $^{51}\text{Cr}$  and  $^{48,49}\text{V}$  are also co-produced but can be chemically separated from the  $^{52}\text{gMn}$  product. Deuteron irradiations of chromium to produce  $^{52}\text{gMn}$  via the  $^{52}\text{Cr}(d,2n)^{52}\text{Mn}$  reaction have also been suggested, but require deuterons of higher energies than are typically available (25→8 MeV).

#### 4.17.2. Targetry and separation chemistry

Commercially available, natural chromium foils or pressed metal powder/pellets make for easy preparation of targets, which can be readily dissolved in HCl following irradiation. The  $^{52}\text{gMn}$  can be isolated by ion exchange chromatography and may include a second purification by solvent extraction [143, 145, 148, 149]. Typically, a strong anion exchange resin is used, the target material is eluted in a weak acid (0.1M HCl or  $\text{H}_2\text{SO}_4$ ) and the  $^{52}\text{gMn}$  can be recovered in acid or in a buffer such as ammonium citrate. If natural composition foils are used, the target material does not have to be recycled.

### 4.18. MOLYBDENUM-99

Molybdenum-99 is the parent nuclide used for generator based production of  $^{99\text{m}}\text{Tc}$ , or, in other words, the most widely used radionuclide globally in diagnostic nuclear medicine (see Section 4.25 for further information regarding  $^{99\text{m}}\text{Tc}$ , including details on direct cyclotron based production). Although  $^{99}\text{Mo}$  is itself generally reactor-produced, the cyclotron based production of  $^{99}\text{Mo}$  as a parent nuclide can be considered as an alternative.

TABLE 19. PROPERTIES OF MOLYBDENUM-99 [150]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Mo-99	65.976 h	$\beta^-$ (100%) $\beta^-_{\text{mean}} = 393 \text{ keV}$	739.5 keV (12.2%)	$^{100}\text{Mo}(p,pn)^{99}\text{Mo}$ $^{100}\text{Mo}(p,2p)^{99}\text{Nb} \rightarrow ^{99}\text{Mo}$ $^{98}\text{Mo}(d,p)^{99}\text{Mo}$

#### 4.18.1. Production parameters

Unlike the direct production of  $^{99\text{m}}\text{Tc}$  (see Section 4.25), if instead the parent  $^{99}\text{Mo}$  is being produced, any co-produced undesired  $^{99\text{x}}\text{Tc}$  isotopes can be chemically separated prior to use of the generator (Table 19). Consequently, if producing  $^{99}\text{Mo}$ , the isotopic composition of the molybdenum target is not as critical as it is for the direct cyclotron based production of  $^{99\text{m}}\text{Tc}$ . Nevertheless, enriched molybdenum is desired to maximize yield, minimize waste and facilitate handling post-irradiation [150].

#### 4.18.2. Targetry and separation chemistry

In considering the cyclotron based production of  $^{99}\text{Mo}$ , in contrast to the fission based reactor route, it is important to keep in mind that significant ‘bulk’ cold molybdenum will be present post-irradiation.

Consequently, the chemistry used for separating  $^{99m}\text{Tc}$  from the bulk molybdenum will not directly translate to the standard fission based (i.e. no carrier added)  $^{99}\text{Mo}$  generator scheme that is currently in widespread use at nuclear medicine centres globally. For more details on molybdenum targets and separation of technetium from bulk molybdenum, see Section 4.25.

#### 4.19. NIOBIUM-90g

Although imaging of antibodies calls for radioisotopes that have half-lives on the order of days (e.g.  $^{89}\text{Zr}$ ,  $^{124}\text{I}$ , etc.), the faster pharmacokinetics associated with antibody fragments (i.e. faster clearance) means a better match with isotopes of shorter, though still moderate, half-lives [151] (Table 20). For this purpose,  $^{90g}\text{Nb}$  has been proposed as a candidate PET isotope of moderate half-life, low positron energy and reasonably high  $\beta^+$  branching ratio (albeit with a high intensity of  $\gamma$  emissions).

TABLE 20. PROPERTIES OF NIOBIUM-90g [151]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Nb-90g	14.60 h	$\beta^+$ (51.2%) $\beta^+_{\text{mean}} = 660 \text{ keV}$	1129.224 keV (92.7%)	$^{90}\text{Zr}(\text{p,n})^{90g}\text{Nb}$

##### 4.19.1. Production parameters

The number of publications to date on the production of  $^{90g}\text{Nb}$  for PET is limited. The most investigated route is  $^{90}\text{Zr}(\text{p,n})^{90g}\text{Nb}$  ( $E_{\text{th}} = 6.970 \text{ MeV}$ ) and, most commonly, by proton irradiation of a natural zirconium foil [152]. Although the natural abundance of  $^{90}\text{Zr}$  is only 51.45%, Radchenko et al. [153] reported on achieving radionuclidic purities in excess of 97% at the end of bombardment with minor impurities of  $^{92m}\text{Nb}$  ( $T_{1/2} = 10.2 \text{ d}$ ),  $^{95}\text{Nb}$  ( $T_{1/2} = 35.0 \text{ d}$ ),  $^{95m}\text{Nb}$  ( $T_{1/2} = 3.6 \text{ d}$ ) and  $^{96}\text{Nb}$  ( $T_{1/2} = 23.35 \text{ h}$ ). Use of isotopically enriched  $^{90}\text{Zr}$  would reduce the co-production of the other radioisotopes of niobium. However, more complex target preparation methods would be required.

##### 4.19.2. Targetry and separation chemistry

Niobium-90g targetry is reasonably straightforward if employing a natural zirconium foil, but one of the main challenges of  $^{90}\text{Nb}$  production is the complexity of the separation chemistry to isolate trace niobium from bulk zirconium. Purification methods are described in the literature. However, they are multistep and tend to involve harsh chemicals from a handling perspective. For example, dissolution of the zirconium metal with hydrofluoric acid on ice [151, 154, 155] or aqua regia [156] have been reported.

Separation schemes have included solvent extraction and solid phase separation methods, select examples of which are given below.

- Maiti et al. [156] employed liquid–liquid extraction. Here, the irradiated foil was dissolved, dried down and residue redissolved in HCl. Next, using 8M HCl and 0.01M tryoctylamine in cyclohexane, niobium was extracted from the zirconium and finally, niobium was back-extracted using 0.1M DTPA/0.1M NaOH.
- Radchenko et al. [151] reported a combined liquid–liquid extraction and solid phase extraction whereby, following hydrogen fluoride (HF) dissolution, 10M HCl and saturated boric acid were added, upon which the niobium fraction was extracted with 0.02M N-benzoyl-N-phenylhydroxylamine (BPHA) in

CHCl<sub>3</sub>, washed with 9M HCl/0.001M HF and 9M HCl and back-extracted with aqua regia. Finally, after evaporating to dryness and redissolving in 0.25M HCl/0.1M oxalic acid, trace amounts of zirconium were further removed by means of an anion exchange column.

- As liquid–liquid extraction is difficult to automate, Radchenko et al. [153] recently reported on a crude two-column purification (i.e. cation, then anion) followed by a final purification on uranium and tetravalent actinide (UTEVA) resin.

Similar to zirconium, niobium has also been reported to form stable complexes with desferrioxamine (DFOA) under moderate conditions [154]. Thus, it is easy to exchange <sup>90</sup>Nb for molecules otherwise labelled with <sup>89</sup>Zr. Use of high grade reagents and avoidance of metal contact materials is important to minimize contamination of metals, such as iron, which may compete with DFOA.

#### 4.20. PALADIUM-103

Paladium-103 decays by EC to <sup>103m</sup>Rh ( $T_{1/2} = 56.114$  m) following de-excitation through isomeric transition. Auger electrons and X rays are emitted as a result of these decay processes (EC and isomeric transition), which can be suitable for cancer therapy. For every 100 decays of <sup>103</sup>Pd, approximately 263 Auger electrons and 188 low energy conversion electrons are emitted [157]. These unique decay features, and the fact that practically no gamma rays are emitted throughout the decay chain of <sup>103</sup>Pd, render this radioisotope particularly suitable for interstitial brachytherapy using encapsulated millimetre-size seed implants for the therapy of prostate [158] and breast cancer [159] or choroidal melanomas [160] (Table 21).

TABLE 21. PROPERTIES OF PALADIUM-103 [9]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Pd-103	16.991 d	EC (100%)	39.748 keV (0.0683%)	<sup>103</sup> Rh(p,n) <sup>103</sup> Pd

##### 4.20.1. Production parameters

The easiest way to produce <sup>103</sup>Pd is through the <sup>103</sup>Rh(p,n)<sup>103</sup>Pd nuclear reaction [161]. Rhodium is a monoisotopic element; thus, no enrichment is required in order to achieve high yields. The impact energy of the protons needs to be less than 20 MeV, in order to minimize the co-production of <sup>101</sup>Pd ( $T_{1/2} = 8.47$  h), <sup>102</sup>Rh ( $T_{1/2} = 207.3$  d) and <sup>102m</sup>Rh ( $T_{1/2} = 3.742$  y) [9].

##### 4.20.2. Targetry and separation chemistry

Various targets have been used for <sup>103</sup>Pd production, but for practical reasons the majority have been in the form of metallic rhodium. Rhodium can be electroplated onto appropriate target backings [9], or alternatively rhodium wires can be directly irradiated and cut to the appropriate length required for seed production.

Paladium-103 seeds are typically prepared by electrodeposition of <sup>103</sup>Pd or exchange reactions. After the irradiation of the target, the irradiated rhodium has to be dissolved and <sup>103</sup>Pd separated from it. Dissolution of rhodium is not an easy task due to its chemical inertness. Various strategies have been developed, among which the most successful are dissolution by sodium bisulphate fusion, gold tetrachloroaurate oxidation, dissolution in HCl and centrifugal electrodisolution technology [9].

Once the target is dissolved,  $^{103}\text{Pd}$  can be separated from the rhodium matrix using solvent/solvent extraction, anion or cation exchange chromatography, controlled cathode potential electrolysis or thermal diffusion [9].

#### 4.21. PLATINUM-191

Platinum has useful properties as a radioisotope for therapeutic applications. Historically, platinum drugs (e.g. cisplatin, carboplatin and oxaliplatin) have generally been used as the first choice in certain anticancer treatments.  $^{191}\text{Pt}$ -cisplatin has been used to inhibit tumour growth and was more effective than non-radioactive cisplatin [162]. Comparing mice treated with cisplatin or  $^{191}\text{Pt}$ -cisplatin, no significant differences in weight change and no differences in mortality were observed. These results imply that  $^{191}\text{Pt}$ -cisplatin is a more effective drug than non-radioactive cisplatin in retarding tumour growth on nude mice without adding systemic toxic effects. Another study in rats on the effect of incorporating  $^{191}\text{Pt}$  into cisplatin showed no difference in toxicity with the incorporation of the radionuclide [163].

TABLE 22. PROPERTIES OF PLATINUM-191 [164]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Pt-191	2.8 d	$\beta^-$ (100%)	n.a. <sup>a</sup>	$^{191}\text{Ir}(p,n)^{191}\text{Pt}$

<sup>a</sup> n.a.: not applicable.

##### 4.21.1. Production parameters

The cross-section and yields of this reaction have been studied in the literature [164, 165]. The use of a natural iridium target resulted in the co-production of  $^{189}\text{Pt}$  and  $^{193}\text{Pt}$ . However, it is possible to produce  $^{191}\text{Pt}$  with high yield and high radionuclidic purity using a highly enriched iridium target in an optimal energy range [164] (Table 22).

##### 4.21.2. Targetry and separation chemistry

Platinum can be separated from the target materials and the other produced radionuclides using solvent extraction [166]. Platinum and palladium are extracted simultaneously into chloroform as they form complexes with diphenylthiourea in 6M HCl solution. The platinum can be subsequently extracted into an aqueous phase from chloroform. Recent development efforts [167] have explored alkali fusion targets with purification steps including both solvent extraction and anion exchange.

#### 4.22. RHENIUM-186g

Rhenium-186g is a beta emitter with applications in targeted radiotherapy as an analogue of the diagnostic radioisotope  $^{99\text{m}}\text{Tc}$ . While historically  $^{186\text{g}}\text{Re}$  has been produced in a reactor via the  $^{185}\text{Re}(n,\gamma)^{186\text{g}}\text{Re}$  reaction, this results in a product with low specific activity that is not suitable for targeting receptors present in low abundance. While cyclotron based production routes result in lower yields when compared with neutron capture, production of  $^{186\text{g}}\text{Re}$  via a cyclotron can result in a product with high specific activity. Thus, this route has been investigated at several sites and the produced  $^{186\text{g}}\text{Re}$  used in a number of preclinical studies [168, 169].

TABLE 23. PROPERTIES OF RHENIUM-186g [170, 171]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Re-186g	3.7186 d	EC (7.47%) $\beta^- = 92.59\%$ $\beta^-_{\text{mean}} = 346.7 \text{ keV}$	137.157 keV (9.47%)	$^{186}\text{W}(p,n)^{186}\text{Re}$ $^{186}\text{W}(d,2n)^{186}\text{Re}$

#### 4.22.1. Production parameters

As described further in a recent IAEA publication, IAEA-TECDOC-1945 [54],  $^{186g}\text{Re}$  can be produced by proton bombardment of tungsten via the  $^{186}\text{W}(p,n)^{186}\text{Re}$  ( $E_{\text{th}} = 1.369 \text{ MeV}$ ) or  $^{186}\text{W}(d,2n)^{186}\text{Re}$  ( $E_{\text{th}} = 3.627 \text{ MeV}$ ) reactions (Table 23). While the natural abundance of  $^{186}\text{W}$  is quite high (28.4%), enriched targets are typically used to maximize yields and minimize the production of other (long lived) rhenium isotopes such as  $^{183}\text{Re}$  ( $T_{1/2} = 70 \text{ d}$ ) and  $^{184}\text{Re}$  ( $T_{1/2} = 35 \text{ d}$ ), produced via the  $^{183}\text{W}(p,n)^{183}\text{Re}$  and  $^{184}\text{W}(p,n)^{183}\text{Re}$  reactions, respectively [172]. The yields for the  $^{186}\text{W}(d,2n)^{186}\text{Re}$  reaction are much higher than the proton-induced reaction and this route is to be considered if deuterons of appropriate energy are available [170, 171, 173].

While the production of  $^{186g}\text{Re}$  via the irradiation of osmium targets has been reported [174], there are significant challenges with target preparation. Additionally, these reactions require a higher bombardment energy and result in lower yields. For these reasons this route is not recommended.

#### 4.22.2. Targetry and separation chemistry

Enriched tungsten targets for  $^{186g}\text{Re}$  production can be prepared from tungsten metal, oxides, carbides or sulphides [169, 174, 175]. As the thermal conductivity of the metal is much higher than the other materials, typically higher irradiation currents are possible with the elemental target material and thus higher yields can be achieved.

Rhenium-186g can be recovered from tungsten targets by either wet methods or thermal chromatography (dry distillation) techniques [169, 176]. Wet methods involve the dissolution of the target material followed by ion exchange chromatography or extraction into organic solvents such as methyl ethyl ketone [168, 177]. Thermal chromatography takes advantage of the volatility of perrhenate ( $\text{HReO}_4$ ), which can be sublimated from the target material under an oxygen-containing atmosphere at elevated temperatures ( $1000^\circ\text{C}$ ) and collected in a cold trap ( $<100^\circ\text{C}$ ) [169, 178].

### 4.23. SCANDIUM

The isotopes  $^{43,44g,44m,47}\text{Sc}$  are of interest for the creation of theranostic radiopharmaceuticals using  $^{43,44,44m}\text{Sc}$  for PET imaging and  $^{47}\text{Sc}$  for therapy with extended discussion of these diagnostic and therapeutic nuclides provided in two recent IAEA publications [54, 73]. In particular, the half-lives of the diagnostic radioscandiums,  $^{43,44g}\text{Sc}$ , are well matched with the biological half-lives of many targeted peptides [179–181]. Scandium can form stable complexes with the DOTA chelator widely used in targeted nuclear medicine imaging agents. For these reasons, scandium radioisotopes have been used in many preclinical experiments and several clinical research studies [182, 183].

TABLE 24. PROPERTIES OF SCANDIUM [179, 180, 184, 185]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Sc-43	3.89 h	$\beta^+$ (88.1%) $\beta^+_{\text{mean}} = 476 \text{ keV}$	373 keV (22.5%)	$^{43}\text{Ca}(p,n)^{43}\text{Sc}$ $^{44}\text{Ca}(p,2n)^{43}\text{Sc}$ $^{42}\text{Ca}(d,n)^{43}\text{Sc}$ $^{40}\text{Ca}(\alpha,p)^{43}\text{Sc}$ $^{46}\text{Ti}(p,\alpha)^{43}\text{Sc}$	
Sc-44m	58.6 h	IT (99.0%)	1157 keV (99.9%) — from $^{44g}\text{Sc}$	$^{44}\text{Ca}(p,n)^{44m}\text{Sc}$ $^{43}\text{Ca}(d,2n)^{44m}\text{Sc}$ $^{47}\text{Ti}(p,\alpha)^{44m}\text{Sc}$	Co-produced with cyclotron production of $^{44g}\text{Sc}$ Decays to $^{44g}\text{Sc}$
Sc-44g	3.89 h	$\beta^+$ (94.3%) $\beta^+_{\text{mean}} = 632 \text{ keV}$	1157 keV (99.9%)	$^{44}\text{Ca}(p,n)^{44g}\text{Sc}$ $^{43}\text{Ca}(d,n)^{44g}\text{Sc}$ $^{47}\text{Ti}(p,\alpha)^{44g}\text{Sc}$	Co-produced with cyclotron production of $^{44m}\text{Sc}$ Also available from a $^{44}\text{Ti}$ generator <sup>a</sup>
Sc-47	3.35 d	$\beta^-$ (100%) $\beta^-_{\text{mean}} = 162.0 \text{ keV}$	159 keV (68.3%)	$^{48}\text{Ca}(p,2n)^{47}\text{Sc}$ $^{46}\text{Ca}(d,n)^{47}\text{Sc}$ $^{44}\text{Ca}(\alpha,p)^{47}\text{Sc}$ $^{48}\text{Ti}(p,2p)^{47}\text{Sc}$ $^{50}\text{Ti}(p,\alpha)^{47}\text{Sc}$	Potential therapeutic partner to $^{43,44g,44m}\text{Sc}$ Also, potentially available from a $^{47}\text{Ca}$ generator <sup>b</sup>

<sup>a</sup> See also Table 30.

<sup>b</sup> See also Table 9.

#### 4.23.1. Production parameters

The desired radioisotopes of scandium can be produced via proton irradiation of calcium targets ( $^{43}\text{Ca}(p,n)^{43}\text{Sc}$ ,  $^{44}\text{Ca}(p,2n)^{43}\text{Sc}$ ,  $^{44}\text{Ca}(p,n)^{44m}\text{Sc}$ ,  $^{44}\text{Ca}(p,n)^{44g}\text{Sc}$ ,  $^{48}\text{Ca}(p,2n)^{47}\text{Sc}$ ), deuteron irradiation of calcium targets ( $^{42}\text{Ca}(d,n)^{43}\text{Sc}$ ,  $^{43}\text{Ca}(d,2n)^{44m}\text{Sc}$ ,  $^{43}\text{Ca}(d,2n)^{44g}\text{Sc}$ ,  $^{46}\text{Ca}(d,n)^{47}\text{Sc}$ ); alpha particle irradiation of calcium targets ( $^{40}\text{Ca}(\alpha,p)^{43}\text{Sc}$ ,  $^{44}\text{Ca}(\alpha,p)^{47}\text{Sc}$ ), or proton irradiation of titanium targets ( $^{46}\text{Ti}(p,\alpha)^{43}\text{Sc}$ ,  $^{47}\text{Ti}(p,\alpha)^{44m}\text{Sc}$ ,  $^{47}\text{Ti}(p,\alpha)^{44g}\text{Sc}$ ,  $^{48}\text{Ti}(p,2p)^{47}\text{Sc}$ ,  $^{50}\text{Ti}(p,\alpha)^{47}\text{Sc}$ ) (Table 24). As the natural abundance of many of the calcium and titanium target isotopes is low, typically enriched targets are used to maximize yields and minimize impurities. In some cases, only partial enrichment may be available, which may be problematic for the production of radioisotopes with high radionuclidic purity. During the cyclotron production of  $^{44g}\text{Sc}$ , the production of the longer lived  $^{44m}\text{Sc}$  cannot be avoided. Thus, in some cases production of  $^{43}\text{Sc}$  may be preferred. During the production of  $^{47}\text{Sc}$ , care must be taken in selecting adequate energy of the beam to avoid the production of  $^{46}\text{Sc}$ , an undesirable long lived contaminant that cannot be chemically separated from  $^{47}\text{Sc}$ . When considering the use of the  $^{48}\text{Ca}(p,2n)^{47}\text{Sc}$  reaction, the co-production of  $^{48}\text{Sc}$  via the  $^{48}\text{Ca}(p,n)^{48}\text{Sc}$  may be an issue. Scandium-44 may also be obtained from a  $^{44}\text{Ti}$  generator (see Section 4.29) and  $^{47}\text{Sc}$  from a  $^{47}\text{Ca}$  generator (see Section 4.8).

#### 4.23.2. Targetry and separation chemistry

Targets may be prepared from pressed elemental calcium, calcium carbonate or calcium oxide in either enriched or natural isotope abundance [186–189]. When working with elemental calcium, the reactivity of the target material needs to be considered and targets may need to be prepared in a glove box. Additionally,

decomposition of carbonate materials under irradiation conditions needs to be considered. Either titanium metal or titanium oxide materials can be used as target material for the production of scandium radioisotopes. However, isotopically enriched titanium material is typically only available in the oxide form.

Purification of scandium radioisotopes is dependent on the target material used for production. Calcium metal targets rapidly dissolve in water, whereas the carbonate form will dissolve in a weak acid. Following this, the scandium radioisotopes can be separated from the target material using precipitation ion exchange chromatography and/or extraction techniques [189–195].

Titanium targets are more difficult to dissolve and typically require the use of strong acid ( $\text{H}_2\text{SO}_4$ ) under reflux conditions and/or the use of HF. However, an alternative dissolution method using  $\text{NH}_4\text{HF}_2$  and HCl to produce HF in small amounts in situ has recently been proposed [196]. Following target dissolution, the scandium radioisotopes are typically purified using ion exchange chromatography [197, 198]. For enriched titanium and calcium targets, recycling the target material may be required.

#### 4.24. STRONTIUM-82

Strontium-82 is primarily used to generate the PET diagnostic radioisotope  $^{82}\text{Rb}$  with a half-life of 1.3 min, which has been used in myocardial perfusion studies. The short half-life of  $^{82}\text{Rb}$  allows scans to be performed sequentially every 10 min, while minimizing the radiation dose to the patient. Furthermore,  $^{82}\text{Rb}$  has also been employed in renal and blood vessel disease studies. Rubidium-82 undergoes rapid uptake by myocytes, which makes it a valuable tool for identifying myocardial ischaemia in PET imaging. The  $^{82}\text{Sr}/^{82}\text{Rb}$  generator is used in the pharmaceutical industry and is sold commercially. A detailed description of the production and uses of  $^{82}\text{Sr}$  is provided in IAEA Radioisotopes and Radiopharmaceuticals Series No. 2 [117].

TABLE 25. PROPERTIES OF STRONTIUM-82 [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Sr-82	25.55 d	EC (100%)	n.a. <sup>a</sup>	$^{80}\text{Kr}(\alpha,2n)^{82}\text{Sr}$ $^{85}\text{Rb}(p,4n)^{82}\text{Sr}$	Used as a generator for $^{82}\text{Rb}$

<sup>a</sup> n.a.: not applicable.

##### 4.24.1. Production parameters

Although the proton route is by far the most common production route, another possible method for producing  $^{82}\text{Sr}$  is by  $^3\text{He}$  or alpha particle irradiation of krypton gas by the  $^{nat}\text{Kr}(^3\text{He},xn)^{82}\text{Sr}$  and  $^{nat}\text{Kr}(\alpha,xn)^{82}\text{Sr}$  reactions (Table 25). These approaches have been investigated as well [199, 200]. Nuclear excitation functions from 20–120 MeV alpha irradiations were measured on a series of gas cells filled with natural krypton to a pressure of 1–3 bar.

##### 4.24.2. Targetry and separation chemistry

For rubidium target preparation, the following procedure can be used. An aqueous RbCl solution is loaded through a column filled with Purolite S950, lightly crushed to increase the mesh size and equilibrated with 50 mL 0.5M ammonium chloride at a pH of 8. The rubidium is then eluted from the resin column using 0.5M ammonium chloride. The final  $^{82}\text{Sr}$  product is eluted with 50 mL 2M HCl, which is evaporated to dryness. The resulting salts are dissolved in 100 mL 2.0M HCl 70% methanol,

and subsequently the solution is pumped through an AGMP-50 macroporous cation exchange resin column [201].

#### 4.25. TECHNETIUM

Technetium-99m has been the most widely used nuclide globally in diagnostic nuclear medicine for many decades. During this time, a large number of  $^{99m}\text{Tc}$  radiopharmaceuticals have been developed (e.g. cardiac imaging [ $^{99m}\text{Tc}$ ]Tc-MIBI (methoxyisobutyl-isonitrile), bone imaging [ $^{99m}\text{Tc}$ ]Tc-MDP (methyl diphosphonate), white blood cell imaging [ $^{99m}\text{Tc}$ ]Tc-HMPAO (hexamethylpropyleneamine oxime), renal imaging [ $^{99m}\text{Tc}$ ]Tc-MAG3 (mercaptoacetyltriglycine), hepatic imaging [ $^{99m}\text{Tc}$ ]Tc-mebrofenin). Although  $^{99m}\text{Tc}$  is typically acquired from generators, the direct production of  $^{99m}\text{Tc}$  using cyclotrons can be considered as an alternative to reactor based  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator production, with yields that are high enough to provide a suitable amount of activity to cover most local and regional needs. In fact, cyclotron based  $^{99m}\text{Tc}$  received its first market approval by Health Canada in November 2020. A dedicated IAEA report on the cyclotron based production of  $^{99m}\text{Tc}$  investigated production routes, target preparation, target dissolution and separation, and quality control [202]. While  $^{99m}\text{Tc}$  is used for planar or SPECT imaging, given the wide array of technetium radiopharmaceuticals available, the use of  $^{94m}\text{Tc}$  for PET imaging has been investigated.

TABLE 26. PROPERTIES OF TECHNETIUM [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Tc-94m	52.0 min	$\beta^+$ (70.2%) $\beta^+_{\text{mean}} = 1094 \text{ keV}$	871.05 keV (94.2%)	$^{94}\text{Mo}(p,n)^{94m}\text{Tc}$	
Tc-99m	6.0067 h	IT ( $\approx 100\%$ )	140.511 keV (89%)	$^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ $^{98}\text{Mo}(d,n)^{99m}\text{Tc}$	Also available from a $^{99}\text{Mo}$ generator <sup>a</sup>

<sup>a</sup> See also Table 19.

##### 4.25.1. Production parameters

To produce reasonable quantities of  $^{94m}\text{Tc}$  or  $^{99m}\text{Tc}$ , some form of molybdenum target material is required (Table 26). The natural isotopic abundance of molybdenum is  $^{92}\text{Mo}$  (14.53%);  $^{94}\text{Mo}$  (9.15%);  $^{95}\text{Mo}$  (15.84%);  $^{96}\text{Mo}$  (16.67%);  $^{97}\text{Mo}$  (9.60%);  $^{98}\text{Mo}$  (24.39%); and  $^{100}\text{Mo}$  (9.82%). In considering the production of  $^{99m}\text{Tc}$ , it is imperative that isotopically enriched molybdenum is used. Considering, for example, the  $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$  ( $E_{\text{th}} = 7.938 \text{ MeV}$ ) reaction, a minimum enrichment of 99% is often noted. However, this needs to be considered a rough guideline, since depending on the irradiation conditions (e.g. energy and time) and which  $^{9x}\text{Mo}$  isotopes comprise the remainder, vastly different levels of  $^{9x}\text{Tc}$  by-products may be produced. A European Pharmacopoeia monograph on the production of  $^{99m}\text{Tc}$  by the proton irradiation of  $^{100}\text{Mo}$  exists [203], for which specifications are noted based on the radionuclidic purity of the  $^{99m}\text{Tc}$  (i.e. not the  $^{100}\text{Mo}$ ). The practical energy range for the production of  $^{99m}\text{Tc}$  is approximately 10–25 MeV, since below 10 MeV the yields of  $^{99m}\text{Tc}$  will be too low, whereas above 25 MeV the impurities in both radionuclidic and metastable technetium content will increase significantly. For the  $^{98}\text{Mo}(d,n)^{99m}\text{Tc}$  production route, co-production of long lived  $^{98}\text{Tc}$  is unavoidable.

In the context of  $^{94m}\text{Tc}$  production, the  $^{94}\text{Mo}(p,n)^{94m}\text{Tc}$  ( $E_{\text{th}} = 5.168 \text{ MeV}$ ) reaction is the most common. Other production routes are provided in the review by Gagnon et al. [204]. In general, isotopically

enriched  $^{94}\text{Mo}$  is used to maximize both yield and purity. However, proton irradiation of natural abundance molybdenum (e.g. as foil) has been reported for chemistry development and early research studies [205]. The maximum proton energy needs also to be limited to minimize the co-production of  $^{94}\text{Mo}(p,2n)^{93\text{m}}\text{Tc}$  ( $T_{1/2} = 43.5$  m) and  $^{93\text{g}}\text{Tc}$  ( $T_{1/2} = 2.75$  h) ( $E_{\text{th}} = 13.808$  MeV).

#### 4.25.2. Targetry and separation chemistry

To maximize production, solid targets are almost exclusively used for the direct cyclotron production of technetium. However, liquid targets have also been demonstrated [206].

Early efforts on cyclotron production of technetium by irradiation of enriched molybdenum with solid targets used  $\text{MoO}_3$  targets [207, 208]. However, such targets were typically limited in beam currents to  $\sim 5\text{--}10$   $\mu\text{A}$ . As efforts to scale up  $^{99\text{m}}\text{Tc}$  production have progressed, metallic molybdenum targets are deemed essential. While molybdenum is not readily electroplated, various methods for metallic target preparation have been reported [209, 210] and tested with beam currents exceeding 100  $\mu\text{A}$ . The optimal target thickness will depend on the incident proton energy.

Regardless of the target preparation strategy, the direct cyclotron production scheme contains ‘bulk’ cold molybdenum, for which the  $^9\text{Tc}$  must be isolated. Chemistry for the separation of technetium from bulk molybdenum has been well documented over many decades, with strategies including, but not limited to, thermal chromatography [208], liquid–liquid extraction [207] and solid phase extraction [211]. Recycling of the enriched target material is perhaps more straightforward when using the oxide. However, recycling of metallic enriched targets has also been reported [212]. Local expertise and ease of automation need to be considered when selecting the method to be implemented.

#### 4.26. TERBIUM-149

Terbium-149 decays by EC, alpha particle emission and positron emission, hence it is an ideal candidate for theranostic applications [213]. Among all alpha emitters considered for targeted alpha therapy, alpha particles emitted by  $^{149}\text{Tb}$  have the highest average linear energy transfer value ( $142$   $\text{keV}\cdot\mu\text{m}^{-1}$ ) [213], which is crucial for effective cell killing. Terbium is a lanthanide element, meaning that it can easily create stable complexes (in vitro and in vivo) with commercially available chelators such as DOTA and DTPA. Similarly to radio-yttrium, it can be used for the labelling of monoclonal antibodies and peptides. The relatively low energy alpha particles ( $3.967$  MeV) emitted by this radionuclide have a very high radiotoxicity and a short range, thus it can be best used for killing cancer cells in transit or micrometastases with minimum damage to healthy cells [213–217].

TABLE 27. PROPERTIES OF TERBIUM-149 [213]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Tb-149	4.118 h	EC (76.2%) $\beta^+$ (7.1%) $\alpha$ (16.7%)	352.24 keV (29.4%)	$^{152}\text{Gd}(p,4n)^{149}\text{Tb}$

##### 4.26.1. Production parameters

Terbium-149 can be produced by a number of heavy-ion induced nuclear reactions, which have little practical value due to the lack of availability of cyclotrons producing high beam currents of heavy ions of sufficient energy [218]. Only the  $^{152}\text{Gd}(p,4n)^{149}\text{Tb}$  reaction can be considered as a viable production route

(Table 27) with recent experimental  $^{nat}\text{Gd}(p,x)$  excitation functions measured by Ref. [219]. Highly enriched  $^{152}\text{Gd}$  is used as a target material to avoid the co-formation of other radionuclidic impurities and to increase the yield. However, the availability of this material is very limited as the natural abundance of  $^{152}\text{Gd}$  is only 0.2%.

#### 4.26.2. Targetry, irradiation parameters and separation chemistry

It is not possible to deposit lanthanides onto appropriate target backings by electrodeposition; thus, irradiation of metal foils or compacted powder tablets of gadolinium oxide are the only options for  $^{149}\text{Tb}$  production. The thermal conductivity of gadolinium is  $10.5 \text{ W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ , which is very low [95], and the thermal conductivity of compacted oxide powders is even lower. Thus, high beam current acceptance of these targets, which limits the production rates of  $^{149}\text{Tb}$ , cannot be expected. Dedicated target stations suitable for the irradiation of thin foils or compacted powders are required for this purpose.

Chemical separation of lanthanides is one of the most challenging separation processes, since all lanthanides are chemically very similar. Ion exchange chromatography separation using Aminex A5 resin in  $\text{NH}_4^+$ -form (Bio-Rad) and various concentrations of  $\alpha$ -hydroxyisobutyric acid (2-hydroxy-2-methylpropionic acid) at pH5 is known to be suitable for the separation of lanthanides [96].

#### 4.27. THALLIUM-201

Monovalent thallium has almost identical biochemical properties to potassium, and due to its favourable radiophysical properties,  $^{201}\text{Tl}$  is widely used for the imaging of myocardial perfusion (for a long time it was considered a gold standard for this diagnostic procedure) [220, 221]. In recent years its use has decreased due to the increasing availability of alternative  $^{99\text{m}}\text{Tc}$ -labelled tracers for myocardial imaging and better radiophysical properties of  $^{99\text{m}}\text{Tc}$ . However, the use of  $^{201}\text{Tl}$  is expected to continue in some specific cases when it has clear advantages over  $^{99\text{m}}\text{Tc}$  [221], and especially when there are shortages of  $^{99\text{m}}\text{Tc}$  on the market.

TABLE 28. PROPERTIES OF THALLIUM-201 [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Tl-201	3.0421 d	EC (100%)	167.43 keV (10.0%)	$^{203}\text{Tl}(p,3n)^{201}\text{Pb} \rightarrow ^{201}\text{Tl}$

##### 4.27.1. Production parameters

Thallium-201 is almost exclusively produced through the  $^{203}\text{Tl}(p,3n)^{201}\text{Pb} \rightarrow ^{201}\text{Tl}$  production route using 28–30 MeV proton beams (Table 28). Highly enriched  $^{203}\text{Tl}$  is irradiated by proton beams in order to produce the intermediate, short lived  $^{201}\text{Pb}$  ( $E_{\text{th}} = 17.512 \text{ MeV}$ ,  $T_{1/2} = 9.33 \text{ h}$ ). Immediately after the end of irradiation,  $^{201}\text{Pb}$  is separated from the target material  $^{203}\text{Tl}$ , which is reused for the preparation of the next target. After some time (typically after 32 h), as the  $^{201}\text{Pb}$  decays to  $^{201}\text{Tl}$ , another chemical separation is performed, leading to pure  $^{201}\text{Tl}$ . If very high activities of  $^{201}\text{Pb}$  are produced in the target, it is often feasible to perform a second chemical separation of  $^{201}\text{Tl}$  from  $^{201}\text{Pb}$  after adequate grow-in, which increases the overall yield of the production.

#### 4.27.2. Targetry, irradiation parameters and separation chemistry

High power electroplated targets are required for cost effective  $^{201}\text{Tl}$  production. Typically, a copper substrate is pre-plated by a tiny protective gold layer before plating highly enriched thallium. If the subsequent radiochemical separation process can provide for efficient elimination of copper contamination, the gold plating can be omitted, which simplifies the target preparation. For high quality thallium plating, a dedicated electroplating system is required, which is based on alternating saw-tooth shaped current density regulators [1, 9]. This process can provide targets, which can easily withstand beam currents of 300  $\mu\text{A}$  at 30 MeV proton energy. The enrichments of  $^{203}\text{Tl}$ , the effective thickness of the target and proton impact energy must be carefully optimized in order to provide maximum yield with the lowest contamination from the  $^{200}\text{Tl}$  and  $^{202}\text{Tl}$  by-products.

Dissolution of the irradiated  $^{203}\text{Tl}$  is typically performed in flow-through cells using nitric or sulphuric acid at elevated temperatures. If there is no protective gold layer between the copper backing and the thallium layer, the process solution will be contaminated by copper and the purification step will be more complicated. The separation is typically performed by ion exchange chromatography, or by solvent extraction after converting thallium to the  $\text{Tl}^{+3}$  stage and back-extracting into aqueous solution after its reduction to the  $\text{Tl}^{+}$  stage [1, 9].

After the first separation,  $^{203}\text{Tl}$  is purified from copper contamination using controlled cathode potential electrolysis. Thallium is dissolved from the platinum cathode, and after adjusting the pH and ionic strength of the solution, it is used for the preparation of the next targets.

#### 4.28. TIN-117m

With a half-life of 13.9 d,  $^{117\text{m}}\text{Sn}$  is most commonly used for pain reduction in bone metastases as [ $^{117\text{m}}\text{Sn}$ ]Sn-DTPA. Furthermore, it is considered a theranostic nuclide, as it can also be imaged by single photon methods. Recently, [ $^{117\text{m}}\text{Sn}$ ]Sn-DOTA-Annexin has also undergone Phase I and Phase II trials, the goal being to image and treat inflammatory tissues, with an initial focus on vulnerable plaque.

TABLE 29. PROPERTIES OF TIN-117m [222]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Sn-117m	13.9 d	IT (100%)	158.56 (86.4%)	$^{114}\text{Cd}(\alpha, n)^{117\text{m}}\text{Sn}$ $^{116}\text{Cd}(\alpha, 3n)^{117\text{m}}\text{Sn}$ $^{\text{nat}}\text{Sb}(p, x)^{117\text{m}}\text{Sn}$

##### 4.28.1. Production parameters

In considering the production route for  $^{117\text{m}}\text{Sn}$ , Stevenson et al. [222] note reactor based production as being the most common method, either via the  $^{116}\text{Sn}(n, \gamma)^{117\text{m}}\text{Sn}$  or  $^{117}\text{Sn}(n, n')^{117\text{m}}\text{Sn}$  reactions. However, with the target material being chemically identical to the desired product, the bulk tin will significantly hinder the specific activities that may be achieved, and thus the practical use of this route for therapeutic applications is limited.

To produce no carrier added  $^{117\text{m}}\text{Sn}$ , it is key to start with a non-tin based target material. Ermolaev et al. [223] describe the proton irradiation of antimony with incident proton energies ranging from ~60 to ~120 MeV. However, although met with a trade-off in  $^{117\text{m}}\text{Sn}$  yield, it is essential to lower the initial proton energy to below ~60 MeV to limit the co-production of  $^{113}\text{Sn}$  ( $T_{1/2} = 115$  d), which in turn decays to  $^{113\text{m}}\text{In}$  ( $T_{1/2} = 99.476$  m).

Most recently, the  $^{116}\text{Cd}(\alpha,3n)^{117\text{m}}\text{Sn}$  ( $E_{\text{th}} = 20.798$  MeV) route has been proposed (Table 29) [222], for which the use of isotopically enriched  $^{116}\text{Cd}$  is required to prevent the co-production of the above noted  $^{113}\text{Sn}$ . Stevenson et al. noted the  $^{116}\text{Cd}(\alpha,3n)^{117\text{m}}\text{Sn}$  route as leading to the highest reported specific activity product compared with other production strategies. An alternative alpha based production route includes the  $^{114}\text{Cd}(\alpha,n)^{117\text{m}}\text{Sn}$  ( $E_{\text{th}} = 5.448$  MeV) reaction. However, the yields for this route are roughly an order of magnitude lower than for the  $(\alpha,3n)$  scheme.

Regardless of the production scheme, it is likely to be advantageous to leave the target in place for several hours to a day post-irradiation to allow for decay of short lived co-produced nuclides.

## 4.28.2. Targetry and separation chemistry

### 4.28.2.1. Antimony based targets

Previously described antimony based targets for the high energy proton based production of  $^{117\text{m}}\text{Sn}$  include hermetically sealed capsules (graphite or stainless steel) of  $\sim 20$  g of Sb [223], as described for linear accelerator production, or electroplated antimony targets for cyclotron based irradiation [222]. Following the dissolution of antimony targets with HCl with gradual addition of  $\text{HNO}_3$ , separation of  $^{117\text{m}}\text{Sn}$  from antimony is reported [208] using a two step approach, namely liquid–liquid extraction of antimony with dibutyl ether, followed by solid phase purification on a silica gel column. Details of volumes were not reported.

### 4.28.2.2. Cadmium based targets

Use of both electroplated [222] and cadmium oxide targets [224] have been described, with high level details of these studies noted below.

For the electroplated cadmium targets, both HCl and  $\text{HNO}_3$  dissolution schemes were investigated, in which  $\text{HNO}_3$  proved more efficient. In either case, the dissolved material was then dried down and the residue taken up in  $\leq 8$  mL 9M HCl. Two columns of AG1-X4 strong base anion exchange resin were used for purification (the first as a bromated column). Note that this separation scheme involves resins of  $\sim 100$ – $200$  g and several steps of rotary evaporation with volumes on the order of  $\sim 1$ – $4$  L.

For the cadmium oxide targets, the irradiated target material is dissolved in concentrated  $\text{HNO}_3$ , filtered through a  $5 \mu\text{m}$  filter and then converted to the fluoride form by addition of HF before evaporating nearly to dryness. The HF addition/drydown is processed three times, the solution is then passed through a DOWEX 1X8, fluorine form, 400 mesh anion exchange resin. Cadmium is eluted with 0.1M HF and the  $^{117\text{m}}\text{Sn}$  with 3M  $\text{HNO}_3$ .

## 4.29. TITANIUM

Titanium-45 is a positron emitting radionuclide of interest as a short lived radiometal imaging isotope, and  $^{44}\text{Ti}$  is of interest as a parent for use in a generator for the production of  $^{44}\text{Sc}$ . While the focus of this section is on  $^{45}\text{Ti}$ , see Section 4.23 or Ref. [73] for more information on the uses of  $^{44}\text{Sc}$ , or details regarding the  $^{44}\text{Ti}/^{44\text{g}}\text{Sc}$  generator.

While  $^{45}\text{Ti}$  has many advantages, such as offering a monoisotopic target material, a high positron branching ratio and a half-life that matches the biological half-life of peptides and antibody fragments, the radiochemistry of  $^{45}\text{Ti}$  is less developed than that of some of the other radioisotopes discussed, particularly in the availability of in vivo stable chelators. For these reasons,  $^{45}\text{Ti}$  has been used in only a limited number of radiochemistry and preclinical imaging studies [183, 225–229].

TABLE 30. PROPERTIES OF TITANIUM [230]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Ti-44	59.1 y	EC (100.0%)	78.3 keV (96.4%)	$^{45}\text{Sc}(p,2n)^{44}\text{Ti}$	Generator for $^{44\text{g}}\text{Sc}$
Ti-45	184.8 min	$\beta^+$ (88.8%) $\beta^+_{\text{mean}} = 439 \text{ keV}$	720 keV (0.154%)	$^{45}\text{Sc}(p,n)^{45}\text{Ti}$	

#### 4.29.1. Production parameters

Both  $^{44}\text{Ti}$  and  $^{45}\text{Ti}$  can be produced by irradiation of natural scandium. Radioisotopically pure  $^{45}\text{Ti}$  can be produced by using proton irradiation energies of <14 MeV, whereas  $^{44}\text{Ti}$  can be produced at higher energies [230] (Table 30). When using the high energy irradiations to produce  $^{44}\text{Ti}$ , several radioscandiums may be co-produced. However, these can be chemically separated from the product and are thus not a concern.

#### 4.29.2. Targetry and separation chemistry

Targets are composed of commercially available scandium foils. Scandium can be easily dissolved in 6M HCl and the  $^{45}\text{Ti}$  or  $^{44}\text{Ti}$  can be isolated by anion exchange chromatography [231]. Previous studies using an anion exchange resin eluted with 6M HCl noted high recoveries (i.e. >99%) [225, 226]. More recent studies, using a hydroxamate resin, elution of the target material in HCl and elution of the radiotitanium in a solution of a weak chelator such as oxalic or citric acid, have also reported excellent separation and good recoveries [231–234]. Another recently reported alternative separation method combined the  $^{45}\text{Ti}$  purification and radiolabelling on a Hypogel 200 1,3-diol resin column [228]. A solvent-free thermochromatographic separation method that requires heating of a scandium target under chlorine gas, with trapping of [ $^{45}\text{Ti}$ ]  $\text{TiCl}_4$ , has also recently been demonstrated [235]. Regardless of the processing method, a solvent-free thermochromatographic separation method that requires heating of a scandium target under chlorine gas, with trapping of [ $^{45}\text{Ti}$ ]  $\text{TiCl}_4$ , has also recently been demonstrated [235]. Regardless of the processing method, as the target material is naturally monoisotopic, recycling is not necessary.

### 4.30. YTTRIUM-86

Quantitative imaging of the biodistribution of therapeutic radiopharmaceuticals enabling the determination of patient-specific doses delivered to critical organs and tumours is the key to successful radionuclide therapy. In many cases there is no straightforward way of imaging the distribution of the therapeutic radionuclide, as in the case of  $^{90}\text{Y}$ , being a pure beta emitter (although it has a small amount of pair production). However, following the principle of theranostics, the imaging can be performed prior to the therapy using the same radiopharmaceutical, labelled with a different radionuclide of the same element. Thus,  $^{86}\text{Y}$  is an ideal radionuclide pair to  $^{90}\text{Y}$  and has been recommended for individual  $^{90}\text{Y}$  dose determination [236]. The decay properties of  $^{86}\text{Y}$  are not ideal for PET imaging due to several high energy gamma-lines co-emitted with the positrons leading to dosimetry concerns. Still, the applicability of this theranostics pair has been validated [237].

TABLE 31. PROPERTIES OF YTTRIUM-86 [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Y-86	14.74 h	EC (68.1%) $\beta^+$ (31.9%) $\beta^+_{\text{mean}} = 660 \text{ keV}$	1.076.63 keV (82.5%)	$^{86}\text{Sr}(p,n)^{86}\text{Y}$

#### 4.30.1. Production parameters

As described in further detail in a recent IAEA publication, IAEA-TECDOC-1955 [73],  $^{86}\text{Y}$  can be produced via the  $^{86}\text{Sr}(p,n)^{86}\text{Y}$  nuclear reaction using small medical cyclotrons ( $E_{\text{th}} = 6.093 \text{ MeV}$ ) (Table 31) [1]. Highly enriched  $^{86}\text{Sr}$  is needed as a target material, in order to prevent the co-production of other long lived yttrium radionuclides;  $^{87}\text{Y}$  and  $^{88}\text{Y}$  being the most critical. It is unavoidable that the short lived  $^{86\text{m}}\text{Y}$  ( $T_{1/2} = 47.4 \text{ m}$ ) is co-produced. Thus, before the radiochemical separation of yttrium from strontium, the decay of this radionuclide needs to be considered, which would also increase by isomeric transition decay the overall yields of  $^{86\text{g}}\text{Y}$ .

#### 4.30.2. Targetry, irradiation parameters and separation chemistry

Metallic strontium is not suitable for target preparation, hence carbonate or oxide of strontium are used as common targets. Typically, the carbonate or oxide powder is compacted using a hydraulic press into a recess in the target backing prior to irradiation. To prevent losses of the target material, often a thin protective foil is placed in front of the target. Carbonate tends to degrade in beam releasing  $\text{CO}_2$ , leading to target failures due to changes in the crystal structure resulting in loss of the mechanical strength of the compacted structure. Thus, the usage of strontium oxide is preferred. Still, the production yields are quite limited since these targets can rarely withstand beam currents above  $20 \mu\text{A}$ . Alternatively, solution targets using a dissolve strontium nitrate salt have been reported [238, 239].

Strontium carbonate and oxide can easily be dissolved in diluted acids after irradiation. Separation of yttrium from strontium and purification of the yttrium product can be performed either by precipitation of strontium followed by filtration [4], electrochemical separation [240–243] or ion exchange chromatography [244]. In either case,  $^{86}\text{Y}$  will be obtained in a form suitable for labelling of monoclonal antibodies or peptides modified with suitable chelators.

Regardless of the separation process used for  $^{86}\text{Y}$  purification, the enriched  $^{86}\text{Sr}$  is ideally recycled. Typically, strontium is precipitated as carbonate and dried before preparing the carbonate target. If oxide is to be used as a target, strontium carbonate needs to be converted to oxide by exposing the carbonate precipitate to temperatures above  $1100^\circ\text{C}$ . The sintered oxide must be ground to a powder before it can be compacted into the form of a target.

### 4.31. ZINC

Zinc is an essential metal in the body, since it is involved in more than 300 metabolic enzymic processes and plays a fundamental role in protein structure and protein–protein interactions. Zinc may play an important role in several diseases and in certain types of cancer, including pancreatic cancer, prostate cancer and breast cancer [245, 246]. Zinc has also been associated with the aggregation of beta amyloid in the brains of Alzheimer’s disease patients [246]. Zinc-62 can also be used as a generator for  $^{62}\text{Cu}$  (Table 32), which has been used to assess hypoxia [247].

TABLE 32. PROPERTIES OF ZINC [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction	Comments
Zn-62	9.186 h	$\beta^+$ (8.2%) $\beta^+$ <sub>mean</sub> = 260 keV EC (91.6%)	596.56 keV (26%)	$^{63}\text{Cu}(p,2n)^{62}\text{Zn}$	Often used as a generator for $^{62}\text{Cu}$
Zn-63	38.5 min	$\beta^+$ (92.7%) $\beta^+$ <sub>mean</sub> = 992 keV EC (7.8%)	669.92 keV (8.0%)	$^{63}\text{Cu}(p,n)^{63}\text{Zn}$	

#### 4.31.1. Production parameters

The cross-section data for the production of the zinc radioisotopes are well studied [248]. The radioisotopes of zinc are typically produced by irradiating copper either in solution [245] or as a copper foil [249, 250]. For the use in humans, target material of isotopically enriched  $^{63}\text{Cu}$  is required in order to avoid the production of  $^{65}\text{Zn}$  with a 244 day half-life from the  $^{65}\text{Cu}(p,n)^{65}\text{Zn}$  nuclear reaction.

#### 4.31.2. Targetry and separation chemistry

When elemental copper is used as the target material, the copper can be dissolved in a mixture of HCl and  $\text{H}_2\text{O}_2$ . This solution can be added to a DOWEX resin column and the copper washed off while the zinc remains on the column [249, 250]. When a liquid copper solution is irradiated, the solution is loaded onto an AG 50W-X8 column at a flow rate of approximately 2 mL/min. The column is washed with 9 mL of water to remove by-products formed during the irradiation [245]. The  $^{63}\text{Zn}$  is eluted off the column with 0.05M HCl in 90% acetone (30 mL) and transferred to a 100 mL neutralization flask for preparation of the solution for human use [245]. For the preparation of the  $^{62}\text{Zn}/^{62}\text{Cu}$  generator, the  $^{62}\text{Zn}$  is loaded onto an AG 1-X8 anion exchange resin column. In 2M HCl, an anionic complex of Zn is formed and is strongly bound by the resin. This solution is used to prepare a generator where the  $^{62}\text{Cu}$  is eluted off the column in a solution of HCl and NaCl, which is used for the subsequent chemistry [251].

#### 4.32. ZIRCONIUM-89g

Zirconium-89g ( $T_{1/2} = 78.4$  h) is a longer lived positron emitting radionuclide well suited for imaging the biodistribution of radiolabelled antibodies. Many groups have successfully shown the use of this isotope in both preclinical and clinical research studies [252–256]. Typically, antibodies are conjugated with the chelator deferoxamine, which allows for relatively straightforward radiolabelling, although other chelators are under development [257–259]. Alternatively,  $^{89}\text{Zr}$  can be used to label DOTA-based tracers when using, for example,  $^{89}\text{Zr}$  in chloride versus oxalate forms.

TABLE 33. PROPERTIES OF ZIRCONIUM-89g [1]

Isotope	Half-life	Decay mode	Highest abundance gamma	Nuclear reaction
Zr-89g	$T_{1/2} = 78.4$ h	$\beta^+$ (22.7%) $\beta^+$ <sub>mean</sub> = 395 keV	909 keV (99%)	$^{89}\text{Y}(p,n)^{89}\text{gZr}$

#### 4.32.1. Production parameters

Zirconium-89g is typically produced via the  $^{89}\text{Y}(p,n)^{89g}\text{Zr}$  reaction using natural yttrium that is monoisotopic (Table 33). Production via the  $^{89}\text{Y}(d,2n)^{89}\text{Zr}$  reaction is possible but has not been explored. Targets of dissolved yttrium salts have been reported but result in significantly reduced yields due to the decreased target atom density, heating and target chemistry [260]. Care must be taken to keep the proton energy below 13.5 MeV to prevent the co-production of  $^{88}\text{Zr}$  ( $T_{1/2} = 83.4$  d), which is an undesirable contaminant produced via the  $^{89}\text{Y}(p,2n)^{88}\text{Zr}$  reaction that cannot be chemically separated from the final product.

#### 4.32.2. Targetry and separation chemistry

Targets can be liquid or solid composed of yttrium foil, pressed powder or sputtered yttrium, and have been used for the production of  $^{89}\text{Zr}$  [261, 262]. Following irradiation to recover the  $^{89}\text{Zr}$  in oxalate form, the yttrium target material is dissolved in HCl (typically 2M) and loaded onto a hydroxamate resin (either synthesized in-house or purchased commercially) for purification [262, 263]. The yttrium target material is eluted in 2M HCl, the resin is washed with water and the  $^{89}\text{Zr}$  is eluted in oxalic acid (0.1–1M). Separation strategies must be adapted when alternative counterions such as chloride or phosphate are desired [264]. As the yttrium target material is naturally monoisotopic, target material recycling is not necessary. Recently, several groups have reported on the development of automated modules for the purification of  $^{89}\text{Zr}$  in larger quantities [265, 266]. As  $^{89}\text{Zr}$  is typically used to radiolabel receptor specific targeting molecules, care must be taken to avoid the introduction of cold metal contaminants, which will reduce the effective specific activity. Production of larger batches of  $^{89}\text{Zr}$  typically results in higher specific activity than smaller ones.

## 5. CONCLUSION

The ability to produce cost effective radiopharmaceuticals locally could have a significant impact in developing countries. Based on the availability of cyclotron facilities, research into the possible production of new unconventional radionuclides has been continuously requested by the Member States. This publication gives a perspective on the topic for researchers and decision makers at cyclotron facilities who need to plan their future activities in the field, as well as for graduate students and academics interested in radioisotope research. This publication suggests the potential uses of alternative radionuclides for a variety of purposes, and provides information on practical production routes and optimal separation techniques for researchers who may not be familiar with them. If there are times when the cyclotron is idle in a facility, research into the production and use of these radionuclides, which are easily produced on most cyclotrons, might be a very valuable use of this time.

In this publication, 31 possible radioisotope production schemes from existing facilities have been described, with the aim of improving knowledge of the alternative uses for cyclotrons in order to increase production and to encourage relevant research for possible clinical trials of these lesser known alternative radionuclides. The preferred production routes for alternative cyclotron based radionuclides with high radionuclidic purity, high yields and, most importantly, high specific activity are explored. High specific activity and the avoidance of contaminants in radionuclide production are mandatory for most current biomedical applications. Different methods are given in this publication that ensure the quality of products. Optimized production, purification and separation methods have enabled the development of several new agents, and preclinical and clinical trials with these compounds are very promising. Future studies are likely to involve the further use of very specific molecularly targeted imaging agents to add to the arsenal of tools for the staging, evaluation and assessment of treatment response in many disease areas.



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## ABBREVIATIONS

DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DTPA	diethylenetriaminepentaacetic acid
EC	electron capture
HF	hydrogen fluoride
MIBG	metaiodobenzylguanidine
PET	positron emission tomography
PSMA	prostate-specific membrane antigen
SPECT	single photon emission computed tomography



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