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MEDICAL RADIONUCLIDE PRODUCTION

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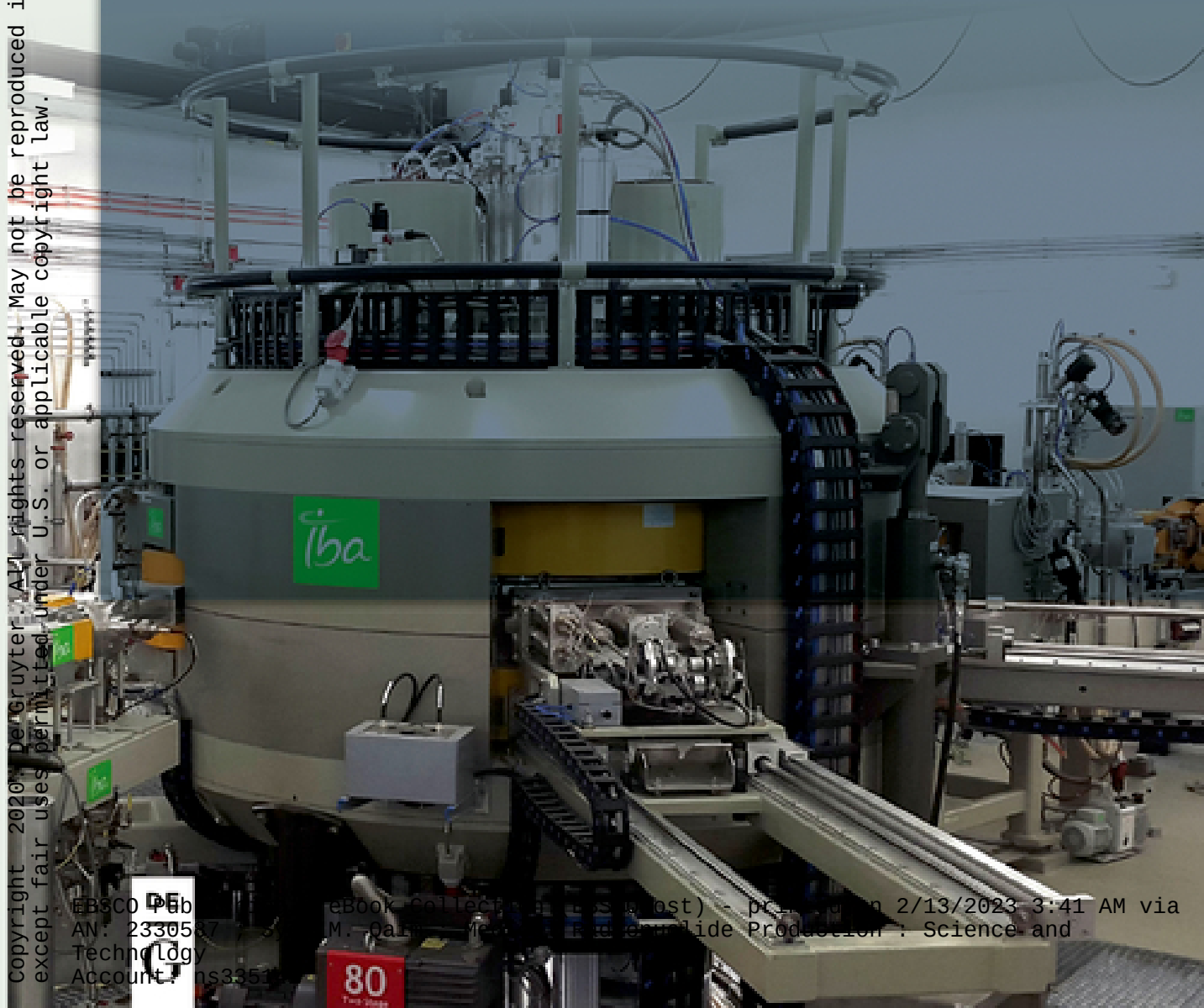

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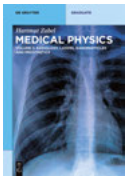

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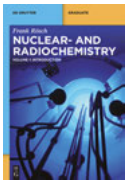

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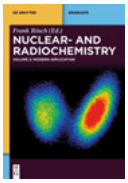

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Medical Radionuclide Production

Science and Technology

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Author
Prof. Dr. Dr. h. c. mult. Syed M. Qaim
Forschungszentrum Jülich GmbH
Institut für Neurowissenschaften und Medizin
INM-5: Nuklearchemie
Wilhelm-Johnen-Str. 1
52425 Jülich
s.m.qaim@fz-juelich.de

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Preface

Radionuclides find application in many areas. Their major use, however, is in medicine, both for diagnosis and internal radiotherapy. The production technology of commonly used standard radionuclides is well established. Yet there is a constant need to develop novel radionuclides, which are opening up new avenues in clinical research.

This book deals with the production of some useful or potentially useful medical radionuclides. It is an extended version of a special lecture course developed and taught by the author for more than 15 years to students of nuclear chemistry at the University of Cologne, Germany and to students of a course "European Master in Nuclear Applications (EMiNA)" at the Aachen University of Applied Sciences (FH) in Jülich, Germany. In a condensed form the lecture course was also held at a few foreign universities and international summer schools. Thus, the first few chapters of the book deal with the related science (i.e. nuclear data, irradiation techniques, chemical processing and quality assurance of the product) in a coherent way. Then follows a description of production methods of commonly used standard radionuclides at nuclear reactors and cyclotrons. More emphasis is, however, on development of novel radionuclides using cyclotrons for applications in positron emission tomography (PET) and internal targeted radiotherapy. The author and his research group at the Forschungszentrum Jülich have been actively engaged in this area of research for more than 30 years, and some of the reported results provide firsthand information on the methodologies developed. The future perspectives of this fast developing technology are also discussed. The book is supplemented by seven review articles periodically written by the author. They should shed some light on the historical development of the field.

Several earlier books on nuclear chemistry and radiopharmaceutical chemistry contained chapters on medical radionuclide production. In this book, an attempt has been made to present a detailed and balanced overview of the basic science and technology involved. The approach is to describe the principles and methodologies in a generally understandable way rather than in indulging in intricate technical details of a production process. It is hoped that the book will attract the attention of students, researchers, technologists and others interested in this field.

Syed M. Qaim
Institut für Neurowissenschaften und Medizin:
INM-5 (Nuklearchemie)
Forschungszentrum Jülich, Germany
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Acknowledgments

The idea of writing this book emerged in 2016 while celebrating 50 Years of Nuclear Chemistry at the Forschungszentrum Jülich, Germany. The Director of the Institute, Bernd Neumaier, immediately showed keen interest in the proposal and later actively supported it. It is a pleasure to thank him for encouragement and moral support. A considerable part of the scientific and technological work described in this book is based on studies performed at the Forschungszentrum Jülich, utilizing three available cyclotrons (and in the early phase partly the research reactor DIDO). I am grateful to the Founding Director of the Institute, Gerhard Stöcklin, for the great impetus to establish a "Nuclear Data and Radionuclide Production Group". His successor, Heinz H. Coenen, supported those research activities. The contributions of several retired colleagues of the Group, many former Ph.D. students, a large number of visiting research scholars and a few other collaborating scientists from external institutes are acknowledged. The collaborations have been particularly strong with the following institutions: University of Debrecen and ATOMKI (Debrecen) in Hungary, Government College University Lahore and PINSTECH (Islamabad) in Pakistan, Rajshahi University and INST (Dhaka) in Bangladesh, Cyclotron Group of the EAEA (Cairo) in Egypt, and iThemba LABS (Cape Town) in South Africa. In recent years Sandor Sudár, M. Shuza Uddin, Mazhar Hussain and Naveed Aslam contributed appreciably to our nuclear data activities. The occasional counsel extended to me by Julius Csikai, Alex Hermanne, Meiring Nortier, Frank Rösch and Ferenc Tárkányi is gratefully appreciated. The editorial staff of De Gruyter Verlag showed strong interest in this project. This served as a motivating force to me. I am indebted to a few colleagues in the institute, particularly Bernhard Scholten and Ingo Spahn, for some useful discussions. My special thanks are due to Stefan Spellerberg for his painstaking and skilful efforts in preparing the manuscript. Finally, I thank my wife, Anneliese Josefa, for her life-long patience and moral support given to me during all my scientific activities.

Syed M. Qaim

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Contents

1 Introduction

1.1 Historical Background

1.1.1 Use of Natural Radioactivity in Life Sciences

Soon after the discovery of radioactivity by H. Becquerel, M. Curie and P. Curie in 1896 in Paris, France, thoughts started developing at several places about a possible application of this phenomenon in life sciences. Although its external therapeutic use was established empirically rather early, it was Georg von Hevesy, a Hungarian physical chemist, who carried out the first biological experiments with natural radioactivity in 1920s. While working in Copenhagen in 1923, he added a small amount of ThB (^{212}Pb) to the culture solution of a growing plant and, after some period of growth, removed the various parts of the plant, ashed them and measured the radioactivity under an electroscope, thereby showing the movement of lead atoms through the plant. Thus, Hevesy had discovered the concept of metabolic turnover [1]. In 1924, he extracted RaE (^{210}Bi) from RaD (^{210}Pb) and studied the metabolism of Bi in rabbits [2]. However, due to toxicity of heavy metals which were the source of natural radioactivity, Hevesy himself was critical of the application of those metals in biology. He therefore got interested in radionuclides of body constituents that were not available in the 1920s.

1.1.2 Discovery of Artificial Radioactivity and the Dawn of its Medical Use

In 1934, I. Curie and F. Joliot reported from Paris, France, the discovery of artificial radioactivity [3] by characterising the product ^{30}P ($T_{½}$ = 2.5 min, β^+ emitter), formed by the ^{27}Al(α,n)^{30}P reaction in irradiation of Al with α-particles emitted from a ^{210}Po source. Similarly, irradiation of B and Mg yielded two additional radioactive products, namely, ^{13}N ($T_{½}$ = 10.0 min, β^+ emitter) and ^{28}Al ($T_{½}$ = 2.2 min, β^- emitter), produced by the ^{10}B(α,n)^{13}N and ^{25}Mg(α,p)^{28}Al processes, respectively. Further investigations on the formation of radioactive products in irradiations of various elements with α-particles emitted by ^{210}Po (or some other α-emitting radioactive source) were continued. However, because of low energies of the α-particles available for irradiations ($E \leq 5$ MeV), the threshold of the investigated nuclear reaction was barely overcome. For this reason, the reaction cross section (which is defined as the *probability of interaction*) was very low, that is, the product, if at all observed, was in very small amount. Thus, the artificially produced short-lived radioactive products, though very interesting for biological applications, could not be made available for metabolic turnover studies proposed by Hevesy (for early history of artificial radioactivity, cf. [4]).

Parallel to the production of a few radionuclides in irradiations of some light mass elements with low-energy α-particles emitted from a few radioactive nuclei,

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two developments occurred in the 1930s. One was based on the use of the neutron, which was discovered by J. Chadwick in 1932 in Cambridge, UK, and the other one depended on the utilization of a device for accelerating charged particles (termed as *cyclotron*), which was invented by E.O. Lawrence and M.S. Livingston in 1932 in Berkeley, USA. A brief discussion of the two approaches is given below.

Utilization of Small Neutron Sources

Very soon after the discovery of the neutron, E. Fermi and his collaborators designed and prepared the first small neutron source in 1933 in Rome, Italy. It consisted of an encapsulated mixture of ^{226}Ra and a light element, like Be. The α-particles emitted from ^{226}Ra interacted with Be and a neutron was produced via the nuclear reaction ^{9}Be(α,n)^{12}C. The neutron coming out of the encapsulation reacted with the surrounding material and induced radioactivity. Soon thereafter, such sources were made available at several places, for example, Paris, France; Vienna, Austria; Berlin, Germany; Boston, USA and so on. Those neutrons had kinetic energies of a few MeV and they played an important role in the production of medically interesting radionuclides in the mid 1930s, especially via the (n,p) reaction.

Using the Ra/Be neutron source, Fermi et al. studied in 1934 the radioactive products formed in the interactions of neutrons with a large number of elements [5], for example, via the reactions ^{31}P(n,p)^{31}Si ($T_{½}$ = 2.6 h); ^{56}Fe(n,p)^{56}Mn ($T_{½}$ = 2.6 h); ^{75}As(n,γ)^{76}As ($T_{½}$ = 26.4 h); ^{127}I(n,γ)^{128}I ($T_{½}$ = 25.0 min). The given half-lives are the values accepted today. It is known now that, due to the increasing threshold of the (n,p) reaction with the increasing mass of the target nucleus, this reaction can lead to radioactive products in appreciable quantities only in the light mass region; in a heavier mass target nucleus, the thermalised neutron led mainly to the (n,γ) reaction product.

For biological studies with radionuclides produced using a Ra/Be neutron source, O. Chiewitz and G. Hevesy, working in 1935 in Copenhagen, Denmark, irradiated sulfur for several days and the ^{32}P ($T_{½}$ = 14.3 d) formed via the ^{32}S(n,p)^{32}P reaction was chemically separated. The product was free of the target material and its quantity (a few hundred kBq) was sufficient for biological studies. In today's terminology, it was of "relatively good specific activity" (for more discussion of this term, see below). They used that radionuclide for the study of phosphorus metabolism in rats [6]. By that time the Geiger–Müller counter was developed. So the distribution of the radioactivity in various organs of the rat could be easily determined. That study led to the formulation of the "tracer principle" and it is regarded today as the dawn of nuclear medicine. The real progress in medical radionuclide production, however, came after the discovery of fission of uranium [7] by Hahn and Strassmann in 1938 in Berlin, Germany, and subsequent construction of nuclear reactors (with high neutron fluxes) in USA in the 1940s (see below).

Advent of Small Cyclotrons

Small cyclotrons delivering proton and deuteron beams of energies of a few MeV could be used to produce a few short-lived β^+-emitting radionuclides of the light elements already in the 1930s. A few examples are ^{11}C ($T_{½}$ = 20.4 min) through the $^{11}B(p,n)^{11}C$ reaction [8]; ^{13}N ($T_{½}$ = 10.0 min) through the $^{12}C(d,n)^{13}N$ reaction [9]; ^{15}O ($T_{½}$ = 2.0 min) through the $^{14}N(d,n)^{15}O$ reaction [10] and ^{18}F ($T_{½}$ = 109.8 min) through the $^{18}O(p,n)^{18}F$ reaction [11]. Due to the low intensities of the then available charged particle beams, only small quantities of those radionuclides could be produced and the radionuclidic purity of the product was not satisfactory. Nonetheless, several tracer studies in biology could be carried out. Very interesting is the early study by Tobias et al. [12] on ^{11}CO inhalation in humans in order to see its possible metabolism to CO_2 which, however, they could not observe.

Besides the above mentioned short-lived low-mass β^+ emitters, a few longer lived heavier mass β^--emitting radionuclides were also produced using the cyclotron. Three important examples are: ^{32}P ($T_{½}$ = 14.3 d) through the $^{34}S(d,\alpha)^{32}P$ reaction and its initial use in treatment of leukemia [13], ^{131}I ($T_{½}$ = 8.02 d) through the $^{130}Te(d,n)^{131}I$ reaction [14] and its use in the study of metabolism of radioiodine from outside of the body using Geiger–Müller counter [15] and ^{89}Sr ($T_{½}$ = 50.5 d) through the $^{88}Sr(d,p)^{89}Sr$ reaction and its application to cure metastatic bone cancer [16].

1.1.3 Enhanced Availability of Radionuclides through Use of Nuclear Reactors

From 1945 onwards, with the availability of nuclear reactors, a tremendous activity ensued to produce a large number of radionuclides. Although by using a $^{9}Be(\alpha,n)^{12}C$ neutron source only a few radionuclides could be produced in small quantities, in the case of reactor neutrons, the list of radioactive products could be extensively enlarged. The neutron spectral shapes involved, as known today, are given in Fig. 1.1(A) and (B) for an $^{241}Am(Be)$ neutron source [17] and a fission reactor [18], respectively. In the former case, the emitted neutrons have a strong low-energy component, followed by a structured shape beyond 2 MeV, with three relatively strong peaks at 3.1, 5.0 and 7.5 MeV, and the tail extending up to 11 MeV. The fission neutrons, on the other hand, have the maximum at about 0.8 MeV, with a weak intensity tail extending up to about 20 MeV. In a nuclear reactor, however, a lot of low-energy neutrons are also present. One distinguishes empirically four energy groups in a fission reactor neutron spectrum: thermal (0.025 eV); epithermal (0.1–500 eV); medium fast (500 eV–0.5 MeV) and fast (>0.5 MeV). The latter two groups are often collectively described as fast neutrons. The relative contributions of the various groups depend on the reactor configuration and the location of the irradiation point. The most well-defined parts are generally the thermal region and the fast region above about 0.30 MeV. The latter region is generally characterised by multiple foil activation and spectrum unfolding technique.

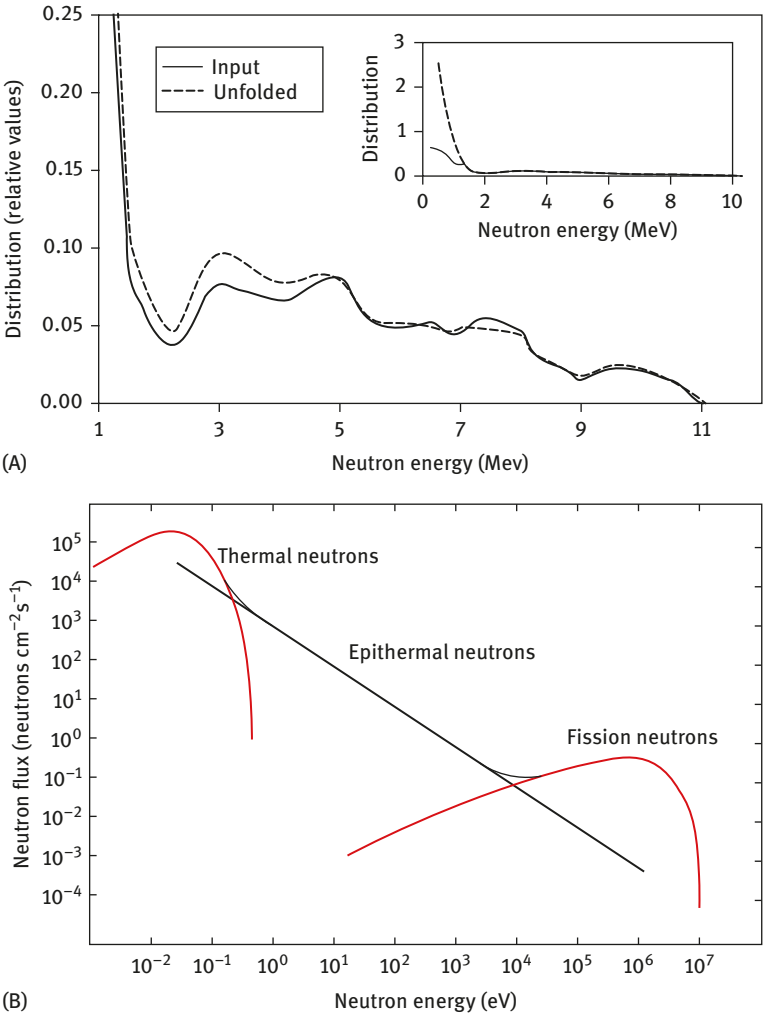

Fig. 1.1: (A) Neutron spectrum from an Am/Be source. The standard input spectrum is compared with an unfolded spectrum. Taken from Uddin et al. [17], with permission from Elsevier. (B) Typical reactor neutron spectrum, taken from Erdtmann and Petri [18], with permission from Wiley-Interscience. The thermal neutrons are useful for the (n,γ) reaction and the fission neutrons for the (n,p) reaction.

Due to high thermal neutron fluxes and high neutron capture cross sections, combined with the relatively high fluxes of fast neutrons above 0.3 MeV, many radionuclides could be produced in a nuclear reactor in sufficient quantities either via the (n,γ) reaction or the (n,p) process. The spectral neutron source given in Fig. 1.1(A) was thus incidentally advantageous for the production of ^{32}P via the ^{32}S(n,p) reaction, utilized by Chiewitz and Hevesy in their pioneering work [6].

In the late 1940s, longer lived β^- emitters tritium, ^{14}C, ^{35}S and ^{32}P became available. They could be transported to long distances from the reactor sites. Furthermore, the practice of labelling drugs and biomolecules with these long-lived "organic" radionuclides made the tracer technique an essential tool in life sciences. Later on, many more radionuclides were produced and their uses in medical diagnosis and radiotherapy were demonstrated. Furthermore, the $^{99}Mo/^{99m}Tc$ and $^{90}Sr/^{90}Y$ generators were developed by Tucker et al. [19] at the Brookhaven National Laboratory, USA. This concept involved the periodic removal of a short-lived decay product from a long-lived parent. This marked the beginning of a new era in nuclear medicine. With the availability of generator systems, short-lived products could be made available even in some remote parts of the world.

1.1.4 Renaissance of the Cyclotron

In the 1950s, the nuclear reactor became a strong source of supply of a large number of radionuclides for medical applications. But the short-lived β^+-emitting radionuclides of organic elements could not be obtained satisfactorily using nuclear reactors. Although many of those β^+ emitters were first produced using a small cyclotron (see above), from late 1940s onwards, the emphasis of cyclotron technology got shifted to building big machines for fundamental studies related to nuclear chemistry and nuclear physics, and the radionuclide production was given very little attention. However, from 1960s onwards, cyclotrons for medical use experienced a renaissance. The activities in support of radionuclide production were tremendously intensified. Several types of compact cyclotrons dedicated to the production of medical radionuclides were developed, especially after the advent of positron emission tomography (PET). Today, radionuclides are produced using both reactors and cyclotrons. With some new development, there may be a shift from one technology to the other, but, in essence, the two technologies are considered as complementary. In the following pages of this book, the science and technology behind the two production methodologies are considered in some detail.

1.2 Radionuclides for Medical Use

1.2.1 General: Types of Applications

Radionuclides find application in many fields; their major use, however, is in medicine, both in diagnosis and therapy [20]. A few radionuclides emitting hard β^- or γ-rays are used as external sources for radiation therapy (e.g., ^{60}Co ($T_{½}$ = 5.3 a), ^{137}Cs ($T_{½}$ = 30.2 a) and ^{192}Ir ($T_{½}$ = 73.8 d)). A few other soft β^- -emitting radionuclides

(tritium, ^{14}C, ^{35}S, etc.), initially used for in vitro investigations, are now mostly utilized in biochemical research. The majority of the radionuclides are administered today into the human body.

The diagnostic use of a radionuclide entails injection of a small amount of radioactivity in the body to be able to investigate the functioning of an organ from outside of the body via tomographic studies. This is called *emission tomography*. The radionuclide for therapy, however, is brought close to the tumour mechanically in the form of a stent, seed or wire. This is called *brachytherapy*. Occasionally the radionuclide in the form of a conglomerate or colloid is inserted into a joint. Although in the former case curative therapy is aimed at by destroying the tumour, in the latter, mostly palliative effect is observed. A more common way of introducing a therapeutic radionuclide in the human body, however, is through a physiological pathway (i.e., *internal radiotherapy*, also known as *open source radiotherapy* or *endoradiotherapy*).

Each of the above mentioned applications demands a special type of radionuclide, the choice being dependent on its decay properties. Furthermore, the chemical form of the injected radionuclide is of paramount importance. A brief discussion of the two considerations (physical and biochemical) in the medical application of a radionuclide is given below.

1.2.2 Physical Considerations

There are two major physical considerations in internal use of radionuclides, namely, suitability for imaging and radiation dose caused to the patient.

Suitability for Imaging

The suitability of a radionuclide for imaging plays a very important role in diagnostic studies. The underlying principle of in vivo medical diagnosis is that the radiation dose to the patient is as low as possible, compatible with the required quality of imaging and the diagnostic advantage in comparison to nonradioactive methods. This is achieved through imaging of the human organ from outside of the body using short-lived radionuclides, emitting predominantly a low-energy γ-ray or a positron. The low-energy γ-ray facilitates *single photon emission computed tomography* (SPECT), and the positron emitter allows PET through detection of the photons generated in its annihilation. The SPECT and PET techniques are collectively known as emission tomography (see above). In contrast to diagnosis, internal radiotherapy stipulates that a certain radiation dose is specifically deposited in a malignant tissue. This is brought about through the use of radionuclides emitting corpuscular radiation, that is, α- or β-particles, or Auger and conversion electrons, in combination with a targeted compound labelled with the radionuclide.

Radiation Dose

The common methodology to calculate the internal dose to the patient from the administered radioactivity was developed by the Medical Internal Radiation Dose Committee (MIRD) of the Society of Nuclear Medicine in the United States of America with its many collaborators and consultants. It is referred to as the *MIRD formalism*. According to the basic formalism [21], the radiation dose $(\overline{D})$ to the patient in gray (Gy) is given by the expression:

$$\bar{D} = 2.13 \cdot \bar{c} \sum_i n_i \cdot \bar{E}_i \cdot \phi_i$$

where $\bar{c}$ is the cumulative concentration of radioactivity $\left(\mathrm{Bq} \cdot \frac{T_{\mathrm{eff}}}{\ln 2} / \mathrm{kg}\right)$, n_i the number of emitted particles or photons per decay, $\bar{E}_i$ the average energy of the emitted radiation, ϕ_i the part of the radiation absorbed in the organ and T_{eff} the effective half-life of the radioisotope in the organ.

Thus, long-lived radionuclides emitting corpuscular radiation (β^- and α-particles), which are completely absorbed in an organ, lead to higher doses. Short-lived radionuclides decaying by electron capture (EC) or by internal transition through γ-ray emission, on the other hand, cause lower radiation doses. In the latter case, however, the additional dose caused by the emitted secondary electrons (conversion or Auger type) has also to be taken into account. Thus, a complete set of radionuclide decay data is needed to calculate the full radiation dose and to decide whether the radionuclide under consideration is suitable for diagnostic or therapeutic studies. Several updated and computerised versions of the MIRD formalism are now available to calculate the dose.

Choice of Radionuclides

Based on physical considerations, the choice of radionuclides for medical applications is thus limited to a maximum of about 80. For SPECT studies, radionuclides decaying by EC or IT and emitting a strong γ-ray in the energy range of 100–250 keV are preferred. The lower γ-ray energy limit is given by the body barrier to be crossed and the upper limit by the efficiency of the detector, which is generally maximum for γ-rays of energies around 150 keV. Two radionuclides, namely, ^{99m}Tc ($T_{1/2}$ = 6.0 h) and ^{123}I ($T_{1/2}$ = 13.2 h), ideally meet those requirements. In PET studies, on the other hand, detection is based on the coincidence events registered for the two 511 keV quanta emitted in the annihilation of the positron. Since the positron emitted from a radioactive nucleus traverses at first a certain length in the tissue before getting thermalised and then destroyed in combination with an electron, the energy of the emitted positron plays an important role. A high-energy positron with a long path length in the tissue affects the resolution of the scan. Similarly, a γ-ray of energy in the vicinity of the annihilation radiation may distort the scan. Furthermore, for obtaining better counting statistics, radionuclides with high positron branchings are

desired. Thus, there are three basic criteria for a positron-emitting radionuclide to be used in PET: low positron energy, high positron intensity and absence of a γ-ray. Incidentally, all three criteria are met in the case of ^{18}F ($T_{½}$ = 109.8 min), which is regarded as a gold standard for PET studies.

As far as internal radiotherapy is concerned, the list of useful and potentially useful radionuclides has been large. Two major considerations are (a) linear energy transfer to the tissue (i.e., eV μm^{-1}) and (b) the range of the corpuscular radiation. In general, previously high-energy β^--emitting radionuclides were used in attempts to destroy the whole large-sized malignant part of the tissue. In recent years, however, the emphasis has been shifting to targeted therapy using low-energy β^- particles, Auger electrons or highly ionizing α-particles, attached to a specific compound. Attention is thus now getting focused on a smaller number of special radionuclides.

1.2.3 Biochemical Considerations

It is basically important that the radionuclide to be used in medicine is in only one chemical form and free of all radioactive and nonradioactive impurities. An efficient chemical processing of the irradiated target is therefore absolutely necessary to remove all non isotopic impurities, and thus to avoid unnecessary radiation and toxicological effects of those impurities. Another consideration is the *specific activity* of the radioactive product (which is defined as the radioactivity per unit mass of the product). It should be as high as possible.

Of greater significance from the biochemical point of view are the following properties:

- Organ selectivity of the radioactive product
- Suitable kinetics in the organ

As is understandable, radionuclides in simple chemical forms are seldom used, some of the exceptions being $^{82}RbCl$ and $^{201}TlCl$ in cardiology, $[^{15}O]O_2$ in oxygen uptake by the brain, and $^{223}RaCl_2$ in blood cancer therapy. In most cases, however, the radionuclide has to be attached to a chemical compound that selectively seeks an organ in the body and its stability in the organ is compatible with the kinetics of the metabolic turnover. Those aspects, however, belong to the realm of radiopharmacy and are beyond the scope of this book. The emphasis here is on radionuclides.

1.2.4 Uniqueness of Radiotracers

A radionuclide in a well-defined chemical form is termed as a *radiotracer*. For medical application, it has to be available in pharmaceutical quality and in sufficient quantity. This requires considerable technical effort, especially if the half-life is

short. Due to the high starting radioactivity and very low mass of the radioactive material involved (~10^{-10} g), efficient and automated/remotely controlled radiochemical processes have to be followed. Nonetheless, the use of the tracer technique in medical diagnosis offers some unique advantages:

- Possibility of dynamic studies from outside of the body
- Biological equilibrium remains undisturbed (allowing use of even toxic material at the subnanoscale level, e.g., ^{201}TlCl)
- Organ imaging can be done at a real molecular level
- Study of physiological function is possible
- Repeated investigations are possible (due to short half-life)

In view of increasing efforts to understand development of certain diseases at an early stage, the use of radiotracer technology appears to be very promising.

1.2.5 Overview of Medical Radionuclides

Many radionuclides are now routinely used in patient care studies, both with regard to diagnosis and internal radiotherapy. Those radionuclides are termed as *standard radionuclides*. A summary of the most commonly used radionuclides is given in Table 1.1. Their decay data have been taken from standard sources [22–24]. They are

Table 1.1: Standard medical radionuclides and their decay data.

Radionuclide	$T_{½}$	Mode of decay(%)	E_{max} of corpuscular radiation: keV	E_{γ}: keV(%)
		Soft radiation emitters		
^{3}H	12.3 a	β^- (100)	18	
^{14}C	5730 a	β^- (100)	156	
^{33}P	25.3 d	β^- (100)	248	
^{35}S	87.5 d	β^- (100)	167	
^{103}Pd	17.0 d	EC (100)	Auger: 17	357.4 (0.0221)
^{125}I	59.4 d	EC (100)	Auger: 18	35.5 (6.7)
		γ-Ray emitters for SPECT		
^{67}Ga	3.26 d	EC (100)	Auger: 7.5	93.3 (38.9); 184.6 (21.4)
^{99m}Tc[a]	6.0 h	IT (100)		140.5 (87.6)
^{111}In	2.81 d	EC (100)	Auger: 19.3	171.3 (90.7); 245.4 (94.1)
^{123}I	13.2 h	EC (100)		159.0 (83.3); 529.0 (1.4)
^{201}Tl	3.06 d	EC (100)		69–82 keV X-rays; 167.4 (10.0)

Table 1.1 (continued)

Radionuclide	$T_{1/2}$	Mode of decay(%)	E_{max} of corpuscular radiation: keV	E_γ: keV(%)
		Positron emitters for PET		
^{11}C	20.4 min	β^+ (99.8) EC (0.2)	960	
^{13}N	10.0 min	β^+ (100)	1190	
^{15}O	2.0 min	β^+ (99.9) EC (0.1)	1720	
^{18}F	109.8 min	β^+ (97) EC (3)	630	
^{68}Ga[b]	1.15 h	β^+ (90) EC (10)	1900	1077.3 (3.2)
^{82}Rb[c]	1.3 min	β^+ (96) EC (4)	3350	776.5 (13.4)
		β^- *and* α*-particle emitters for internal therapy*		
^{32}P	14.3 d	β^- (100)	1710	
^{89}Sr	50.5 d	β^- (100)	1470	
^{90}Y[d]	2.7 d	β^- (100)	2290	
^{131}I	8.02 d	β^- (100)	607	364.5 (81.7), 637.0 (7.2)
^{153}Sm	1.93 d	β^- (100)	808	69.7 (4.8), 103.2 (28.3)
^{177}Lu	6.65 d	β^- (100)	498	113.0 (6.2), 208.4 (10.4)
^{188}Re[e]	17.0 h	β^- (100)	2150	155.0 (15.0), 633.1 (1.25)
^{211}At	7.2 h	α (41.8) EC (58.2)	5869	687.0 (0.246)
^{213}Bi[f]	45.6 min	α (2) EC (98)	5840	440.5 (25.9)
^{223}Ra	11.4 d	α (100)	5697	154.2 (5.7), 269.5 (13.9)
^{225}Ac	10.0 d	α (100)	5750	

[a] Via the generator system $^{99}\mathrm{Mo}(2.75\mathrm{d}) \xrightarrow{\beta^-} {}^{99\mathrm{m}}\mathrm{Tc}$.
[b] Via the generator system $^{68}\mathrm{Ge}(271.0\mathrm{d}) \xrightarrow{EC} {}^{68}\mathrm{Ga}$.
[c] Via the generator system $^{82}\mathrm{Sr}(25.3\mathrm{d}) \xrightarrow{EC} {}^{82}\mathrm{Rb}$.
[d] Via the generator system $^{90}\mathrm{Sr}(28.9\mathrm{a}) \xrightarrow{\beta^-} {}^{90}\mathrm{Y}$.
[e] Via the generator system $^{188}\mathrm{W}(69.8\mathrm{d}) \xrightarrow{\beta^-} {}^{188}\mathrm{Re}$.
[f] Via the generator system $^{225}\mathrm{Ac}(10.0\mathrm{d}) \xrightarrow{\alpha} {}^{221}\mathrm{Fr}(4.9\mathrm{min}) \xrightarrow{\alpha} {}^{217}\mathrm{At}(32.3\mathrm{ms}) \xrightarrow{\alpha} {}^{213}\mathrm{Bi}$.

well known and the relevant production methodologies are also well developed, either at a reactor or at a cyclotron. To the group of "standard radionuclides" also belong several other radionuclides which have been finding very wide application in biochemical research. Those radionuclides emit very soft β^- radiation and do not require elaborate shielding. They are also listed in Table 1.1.

In addition to patient care studies and routine biochemical research using standard radionuclides, continuous and extensive research has been underway for the last three decades to develop some novel radionuclides. In recent years, those efforts have been intensified. The production technology is fast developing and a few radionuclides are now available for preclinical or clinical research. The techniques involved are of interdisciplinary nature and the use of both cyclotrons and accelerators in increasing. The major emphasis is on non-standard positron emitters, as well as on radionuclides emitting low-energy β^- particles and highly ionizing α-particles. Those novel radionuclides and the relevant developing production technologies are discussed in some detail in the later part of this book.

1.3 Some Basic Considerations in Medical Radionuclide Production

Radionuclides for medical applications are obtained either via direct production at a nuclear reactor or a cyclotron, or by using a radionuclide generator system. Detailed considerations of the three methodologies are given in Ref. [25]. In this section, only some basic principles relevant to general understanding are briefly described.

1.3.1 Production at a Nuclear Reactor

General: Classification of Research Reactors

A nuclear reactor is a large facility based on a controlled chain of fission events; it constitutes a strong source of neutrons. Very extensive studies exist on the physics and neutronics of fission reactors. The radionuclide production technology is also well developed [cf. 26]. Here only some salient aspects are discussed.

For radionuclide production different types of research reactors are used. To remove a misconception, it should be clearly stated that nuclear power plants are very rarely utilized for radionuclide production or development work. In the world about 275 research reactors are available and a large number of them are used in some sort of radionuclide production work. They may be classified according to the available neutron flux density, as given in Table 1.2. The radionuclide product yield in a low power reactor is generally low, and high power reactors are used more in fundamental nuclear and materials research rather than for radionuclide production. The major emphasis regarding radionuclide production is thus on the use of medium power reactors. Presently, large-scale production for general world supply of radionuclides is limited to about 10 medium power reactors, some of them reaching approximately the level of high flux reactors, for example, in Petten, Oak Ridge, Demitrovgrad and so on.

Table 1.2: Classification of nuclear research reactors used in radionuclide production.

Parameter	Type of reactor		
	Low power	**Medium power** [a]	**High power**
Power (MW)	<5	6–30	>50
Flux ($n \cdot cm^{-2} \cdot s^{-1}$)	$<10^{14}$	1.0×10^{14}–5×10^{14} [b]	$\geq 10^{15}$

[a] Most commonly used in medical radionuclide production.
[b] A typical neutron flux distribution (n cm^{-2} s^{-1}) at an irradiation position in the 20 MW DIDO reactor at FZ Jülich was: $\phi_{th} = 2.5 \times 10^{14}$; $\phi_{epith} = 6.2 \times 10^{12}$; $\phi_{fast} = 8 \times 10^{13}$.

Formation of a Radionuclide

The formation of a radioactive product in irradiation of a target in a nuclear reactor is described by the following activation equation (in a simplified form):

$$A = N\,\phi\,\sigma\,\left(1 - e^{-\lambda t}\right)$$

where A is the absolute activity of the reaction product (Bq) at the end of irradiation, N the number of target nuclei, ϕ the projectile flux density (cm^{-2} s^{-1}), σ the cross section (cm^2), λ the decay constant and t is the time of irradiation (s). The number of nuclei exposed to projectiles is calculated from the mass of the target used, the irradiation time is properly chosen and λ is a constant. The cross section of a reaction is generally known and the projectile flux has to be determined. The absolute activity of the product is determined experimentally and the obtained value can be compared with the calculated value from the above equation. The level of agreement between the two values reflects the accuracy of σ and ϕ values used. It should, however, be pointed out that in real practice several modifications in the above equation are often necessary to take account of the following factors:

- self shielding in the target,
- power variation in the reactor (change in ϕ),
- burn up of the target material,
- burn up of the product radionuclide through a subsequent (n,γ) process.

Those factors may vary for different target materials being irradiated with neutrons in various energy segments of the neutron spectrum shown in Fig. 1.1(B).

Competing Nuclear Reactions

The most common nuclear processes involved in the interaction of slow neutrons with target nuclei are scattering (elastic and inelastic) and radiative capture. The elastic scattering has no significance in radionuclide production. But the inelastic scattering, that is, the (n,n′γ) process, may lead to the formation of a radioactive isomeric state. The radiative capture, that is, the (n,γ) reaction, on the other hand,

is extensively used in radionuclide production. The major drawback of the above two processes, however, is the low specific activity of the product. Since in an irradiation only a very small fraction of the target nuclide is converted to a radioactive nuclide of the same element, and the large amount of the inactive target nuclide remains unchanged, the radioactivity obtained per unit mass of the element remains low. For many applications, such as brachytherapy, a low specific activity product may be acceptable. But for open-source internal medical applications, generally radionuclides with high specific activity are needed. There are two possibilities of increasing the specific activity:

Szilard–Chalmer's process: This involves the separation of the recoiling radioactive atoms following the (n,γ) reaction (from the bulk of the inactive target material), because they often occur in a different valence state as compared to the target atoms. The specific activity of the separated species is then high, but its yield amounts to only a small fraction of the total activity. The method was previously used in preparation of radioactive products of metals like Cr, but it is now hardly used.

Precursor/generator system: This involves the use of the daughter radionuclide formed via β^- or EC decay of the (n,γ) reaction product. Two important examples are $^{98}\mathrm{Mo}(\mathrm{n},\gamma)^{99}\mathrm{Mo} \xrightarrow{\beta^-} {}^{99\mathrm{m}}\mathrm{Tc}$; $^{124}\mathrm{Xe}(\mathrm{n},\gamma)^{125}\mathrm{Xe} \xrightarrow{EC} {}^{125}\mathrm{I}$.

Besides the (n,γ) reaction, the (n, fission) process is also extensively used, but only in a few highly advanced production laboratories. In general, products lying on one of the two mass-yield peaks of the fission process can be advantageously obtained. Three very important radionuclides, namely, ^{90}Sr ($T_{½}$ = 28.87 a), ^{99}Mo ($T_{½}$ = 2.75 d) and ^{131}I ($T_{½}$ = 8.02 d), are produced via the fission of ^{235}U. The first two are used in generator systems to supply the medical radionuclides ^{90}Y ($T_{½}$ = 2.67 d) and $^{99\mathrm{m}}$Tc ($T_{½}$ = 6.0 h), respectively, and ^{131}I is used directly in internal radionuclide therapy. Another fission-produced radionuclide ^{137}Cs ($T_{½}$ = 30.2 a) is partly used in external radiation therapy. The fission-produced radionuclides are of very high specific activity. The main disadvantage, however, is the extensive chemical processing involved.

A yet another nuclear reaction used for the production of a few special radionuclides in a nuclear reactor is the (n,p) process. This reaction has a certain threshold. Therefore, in general, only the fast part of the fission neutron spectrum (i.e., above about 1 MeV) is effective for the production of the desired radionuclide. This reaction is generally applied in the light mass region where the reaction threshold is low and the competition between charged particle emission and neutron emission is in favour of the former. Two important radionuclides, namely, ^{14}C ($T_{½}$ = 5,730 a) and ^{32}P ($T_{½}$ = 14.3 d) are produced with high specific activity via the $^{14}\mathrm{N}(\mathrm{n},\mathrm{p})^{14}\mathrm{C}$ and $^{32}\mathrm{S}(\mathrm{n},\mathrm{p})^{32}\mathrm{P}$ reactions, respectively. Their yields are fairly high.

It should also be mentioned that in certain cases the charged particle emitted (p or t) in a neutron induced reaction may induce a secondary reaction on a neighbouring nucleus. Protons are created in the interaction of neutrons with hydrogen-containing

compounds and tritons are emitted in the interaction of neutrons with Li-containing compounds. An example is the formation of ^{18}F via the reaction sequence $^{6}Li(n,\alpha)^{3}H \rightarrow {}^{16}O(t,p)^{18}F$. Thus irradiation of Li_2CO_3 leads to the formation of appreciable quantities of ^{18}F. The role of such secondary reactions in production of tracer quantities of a few radionuclides in a nuclear reactor has been recently summarized [27].

1.3.2 Production at a Cyclotron

General: Classification of Cyclotrons

A cyclotron is a charged particle accelerator in which the particles travel in a succession of semicircular orbits of increasing radii under the influence of a magnetic field. They are accelerated at each such orbit by an electric field produced by a high-frequency generator. A large number of low- and intermediate-energy cyclotrons have been constructed over the last 85 years for performing fundamental and applied research. During the last three decades, however, several types of special cyclotrons have been developed to meet the particular demands of medical radionuclide production. They were classified according to their production capacities [28]. An updated summary list is given in Table 1.3.

Table 1.3: Classification of cyclotrons used for radionuclide production.

Classification	Characteristics (charged particle)	Energy (MeV)	Major radionuclides produced
Level I	Single particle (d)	<4	^{15}O
Level II	Single particle [a] (p)	≤12	^{11}C, ^{13}N, ^{15}O, ^{18}F
Level III	Two particle [b] (p, d)	≤20	^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{64}Cu, ^{86}Y, ^{124}I (^{123}I, ^{67}Ga, ^{111}In)
Level IV	Multiple particle [c] (p, d, ^{3}He, ^{4}He)	≤40	^{38}K, ^{73}Se, $^{75–77}Br$, ^{123}I, $^{81}Rb(^{81}Kr)$, ^{67}Ga, ^{111}In, ^{201}Tl, ^{22}Na, ^{57}Co, ^{44}Ti, ^{68}Ge, ^{72}As, ^{140}Nd, ^{211}At, ^{227}Ac
Level V	Single or multiple particle [d] (p, d, ^{3}He, ^{4}He)	≤100	^{28}Mg, ^{52}Fe, ^{67}Cu, ^{72}Se, ^{68}Ge, ^{82}Sr, ^{117m}Sn, ^{123}I
Level VI	Single particle (p)	≥100	^{26}Al, ^{149}Tb, ^{152}Tb, ^{227}Ac, etc.

[a] Some linear tandem accelerators of this energy are also finding limited use.
[b] Most commonly used at PET Centres.
[c] Intense electron linear accelerators ($E \geq 30$ MeV) are also under development to provide high-intensity neutrons or high-intensity and high-energy bremsstrahlung for radionuclide production, the former inducing an (n,γ) reaction and the latter a (γ,p) or (γ,n) reaction.
[d] Intense beams of deuterons ($E \approx 40$ MeV) incident on a Be target provide breakup neutrons ($E \approx 14$ MeV), which could be used for radionuclide production via (n,2n), (n,p) or (n,np) reaction.

The smallest machine (Level I) is a cyclotron that accelerates deuterons only up to 4 MeV, that is, below the breakup threshold of the deuteron (to avoid neutron background and thus concrete shielding). Its utility was demonstrated a long time ago [cf. 29], and it is used exclusively in a hospital environment to produce ^{15}O for PET studies, for example, in Berlin, London, Turku, St. Louis and so on. A small linear two particle (p and d) accelerator with energies below 3.7 MeV has also been developed with the aim of producing ^{15}O and ^{18}F, but its use has been very limited. The next-stage accelerator (Level II) is a single-particle negative ion machine for proton acceleration up to an energy of 11 or 12 MeV. It can be used to produce the four major β^+ emitters, namely, ^{11}C, ^{13}N, ^{15}O and ^{18}F, although the absence of the deuteron beam is somewhat disadvantageous with regard to the production of ^{15}O, and the rather low proton energy gives a low yield of ^{13}N. It has been extensively developed and used in Madison, USA. The next higher group of cyclotrons (Level III) generally comprises two particle machines with $E_p \leq 20$ MeV and $E_d \leq 10$ MeV. It is ideally suited for production of the standard PET radionuclides and has therefore been recently installed at a large number of PET Centres. Many of the non-standard PET radionuclides (discussed later in this book) have also been developed using such a cyclotron. The even higher energy machines (Levels IV–VI) have capabilities of producing many more radionuclides, in particular when, besides p and d, the α-particle beam is also available. On the other hand, when energies above 100 MeV are under consideration, only the proton beam is

Photograph: Partial view of the IBA Cyclotron CPX 30 at the Forschungszentrum Jülich (courtesy FZ Jülich).

of interest. At large research centres generally several cyclotrons exist. At the Forschungszentrum Jülich, for example, four cyclotrons and a beam line at the cooler synchrotron COSY, covering the proton energy range up to 150 MeV, are available for routine production of a few radionuclides as well as for research and development work on novel radionuclides. A recently installed Level IV machine is shown in the photograph. It delivers proton, deuteron and α-particle beam of energy up to 30 MeV.

It should be mentioned that in radionuclide production work, high-intensity beams are absolutely necessary; otherwise, the total batch yield of the product may not be sufficient for application. Thus in contrast to fundamental nuclear science work, the emphasis in radionuclide production is on beam intensity rather than on beam quality, and the above-mentioned cyclotrons, especially the Levels I–IV machines, have been developed with this aim in view.

A passing reference needs also to be made to increasing use of linear tandem accelerators with $E_p \leq 12$ MeV to produce some medical radionuclides. Furthermore, considerable interest is also developing to make use of high-energy bremsstrahlung in medical radionuclide production. A 30 MeV or higher energy electron linear accelerator (LINAC) is used to generate high-intensity neutrons or hard photons that can produce a few special radionuclides, the former inducing an (n,γ) reaction and the latter a (γ,n) or (γ,p) reaction. Attempts are also underway to generate intense fast neutron fields via the d/Be or d/C breakup process and to use that field for production of some radionuclides through an (n,2n), (n,p) or an (n,np) reaction. Thus, there is an overall increase in efforts to produce accelerator-based radionuclides.

Considerable interest has existed in the past in the use of cyclotrons for medical radionuclide production [30], but in recent years it has been rapidly increasing and today, about 1200 cyclotrons are being partly or fully utilized for this purpose [31]. Most of them are Level III machines and are specifically manufactured for PET application in medicine.

Some Special Considerations

While using charged particles (from a cyclotron or an accelerator) in radionuclide production, three special considerations, namely, energy loss in the matter, heat generation and changing cross section, need to be taken into account. Those considerations are discussed below in some detail.

Energy Loss

While traversing a medium, a charged particle loses part of its kinetic energy via excitation and ionization of the surrounding atoms. It is an atomic phenomenon (and not a nuclear reaction where the charged particle is destroyed). In other words, the charged particle continues to lose its energy till it comes to rest. The degradation in energy is described by the well-known Bethe–Bloch equation given below (in a simplified form, i.e., neglecting the density effect correction and the shell correction):

$$-\frac{dE}{dx} = Kz^2 \frac{Z}{A} \frac{1}{\beta^2} \left[\ln \frac{2m_e c^2 \beta^2}{I(1-\beta^2)} - \beta^2 \right]$$

where

$-\frac{dE}{dx}$ is the energy loss per unit length,
K the constant in stopping power (0.3070 MeVcm^2),
z the incident particle charge,
Z the atomic number of absorbing material,
A the molar fraction of absorbing atoms (g mol^{-1}),
β the u/c (relative velocity of the incident particle),
c the velocity of light in vacuum,
m_e the electron rest mass and
I the mean electronic excitation energy of an element (eV).

Thus, the stopping power depends on the charge and velocity of the incident particle as well as on the effective ionization potential and the atomic and mass numbers of the medium. With the decreasing energy of the projectile, the stopping power of the absorber increases, reaching maximum values during the last stages of the energy loss. This is reflected in a peak called the *Bragg peak*. As expected, the energy degradation is higher in solids than in liquids and gases. Thus, for covering a certain energy range of the projectile in a production target, solid material is much more effective; in case of liquids and gases, larger volumes are needed.

It should be noted that although the degradation of the projectile energy is dependent both on the absorbing material and the type of the projectile, the latter has more serious consequences because of the squared dependence on the charge of the projectile. Due to this reason, protons have a much longer path length in an absorber than the α-particles. In practice, it means that the production yield of a radionuclide via an α-particle-induced reaction on a medium or heavy mass nucleus is much lower than that via a proton-induced reaction [cf. 32], even if the α-particle induced reaction cross section is higher.

An accurate calculation of the projectile energy loss in a target plays an important role in the optimisation of a production process because an uncertainty in the calculation influences both the energy scale and the yield of the product. Extensive documentations on range-energy relationships of charged particles in various matters exist in the literature [cf. 33, 34] and well-established codes are available (STACK, SRIM, etc.) for accurate energy loss calculations.

Heat Generation in Target

Charged particles lose energy while traversing a medium. This energy is deposited in the medium and leads to heat generation, the latter depending on the total energy loss of the projectile and its intensity. In fundamental nuclear chemistry work

involving nuclear reaction cross-section measurements, the heat generation is not a problem, since the beam currents used are low (50–500 nA). In real production runs, however, beam currents of up to 1 mA may be used. Heat generation and the incumbent heat transfer then usually become the limiting factors in large-scale production of several radionuclides. Design and construction of highly sophisticated target systems with efficient cooling are therefore absolutely mandatory for meaningful production of radionuclides at cyclotrons.

Changing Reaction Cross Section

The loss in the energy of a neutron traversing a thin target is generally negligible and so the reaction cross section is considered to be practically constant for the target. In the case of a charged particle induced reaction, however, due to the rapid loss of energy of the projectile within the target, a relatively broad range of energies is encountered. Since the reaction cross section is often very sensitive to the incident energy, an average cross section over a chosen energy range cannot be used. Instead a full knowledge of the change in cross section as a function of projectile energy (termed as the *excitation function*) is required. It is therefore incumbent to determine the cross section using a very thin sample where the energy loss is very small. Another difference between work with neutrons and charged-particle beams lies in the geometry and configuration of the system. Although in the case of neutrons one uses the term flux density ϕ (n cm^{-2}s^{-1}), for charged particles it is only flux or current (I = particles s^{-1}). The activation equation given above is then expressed in the form:

$$A = \frac{N_L \cdot H}{M} I \left(1 - e^{-\lambda t}\right) m\sigma$$

where N_L is the Avogadro number, H the enrichment (or isotopic abundance) of the target nuclide, M the mass number of the target element, I the projectile current (particles s^{-1}), m the surface mass of the target material needed to decrease the projectile energy over a very small range (g cm^{-2}: denoted as *surface density*), σ is the cross section at the energy effective in the target and A, t and λ have the same meaning as in the equation for activation with neutrons. Thus, the rapid changes in both the stopping power of the projectile and the cross section of the reaction deserve special attention while calculating the yield of the product over a certain target thickness. For thicker targets, a slightly modified form of the above equation is used to calculate the product activity (see Chapter 2).

Competing Nuclear Reactions

With the increasing energy of a charged particle incident on a target nucleus, several competing reaction channels start opening up, each leading to a different stable or radioactive product. Several of those products may be medically interesting, provided they could be obtained with high purity. As an example, the radioactive

products expected in the interaction of about 70 MeV protons with the isotopically enriched ^{68}Zn are listed in Table 1.4.

Table 1.4: Nuclear reactions induced by protons on ^{68}Zn to produce medical radionuclides.

Reaction product	$T_{½}$	Nuclear reaction	Q-value * (MeV)	Effective energy range (MeV)	Cross section at maximum of the excitation function (mb)
^{68}Ga	1.15 h	^{68}Zn(p,n)	−3.703	8–18	900
^{67}Ga	3.26 d	^{68}Zn(p,2n)	−11.977	15–30	730
^{67}Cu	2.58 d	^{68}Zn(p,2p)	−11.192	30–80	12
^{64}Cu	12.7 h	^{68}Zn(p,αn)	−7.786	15–35	63
		^{68}Zn(p,2p3n)	−36.205	45–100	52

* *Q*-value is defined as the energy released or absorbed in a nuclear reaction. It is calculated from the difference in masses of the reactants and the resultants (in units of energy). By adding the recoil and Coulomb barrier corrections to the *Q*-value, one obtains the threshold of the reaction.

The various reactions with their calculated *Q*-values and the experimentally determined effective energy ranges are given. All four radioactive products, namely, ^{68}Ga, ^{67}Ga, ^{67}Cu and ^{64}Cu are medically interesting and they can all be produced in high purity provided proper proton energy ranges are used and clean chemical separations are performed. The gallium radionuclides can be chemically separated well from the copper radionuclides. Individual production of radionuclides could be achieved through the choice of proton energy ranges in the target; for example, intermediate energy range for the production of ^{67}Ga and low energy range for ^{68}Ga. Similarly intermediate energy range is suitable for the production of ^{64}Cu and higher energy range for ^{67}Cu. The exact energy ranges can and should be derived from the known excitation functions. The point to be emphasized here is that, with the increasing projectile energy, the number of products increases, but the production of several radionuclides with acceptable purity is possible, provided proper conditions are chosen. All those aspects are discussed in some detail in other chapters.

1.3.3 Comparison of Reactor and Cyclotron Production of Radionuclides

General

As discussed above, nuclear reactors and cyclotrons are to be regarded as complementary with regard to medical radionuclide production. However, there are some typical characteristics of each of the two facilities, and also some advantages and disadvantages associated with their use. A brief discussion follows.

The major characteristic of a reactor is that it delivers neutron excess radionuclides that mainly decay by β^- emission and are thus very suitable for internal radionuclide

therapy. In contrast, the major characteristic of a cyclotron is that it supplies neutron-deficient radionuclides, which find application in diagnostic nuclear medicine. Many other radionuclides, for example, γ-ray emitters as well as α-particle and Auger electron emitters, can often be produced using both reactors and cyclotrons.

The major advantage of a reactor is that large quantities of radionuclides can be produced. Since the two commonly used production processes, namely, (n,γ) and (n,f), have generally large cross sections, and since large samples can be irradiated for relatively long times at intermediate to high neutron fluxes, the product batch yields could be very high. For example, the radionuclide ^{99}Mo is regularly produced via the fission process at a few reactors in TBq quantities and supplied to the world for producing ^{99}Mo/^{99m}Tc generators. Some longer lived radionuclides, such as ^{32}P and ^{131}I, are also produced in batches of >100 GBq. In contrast, the batches of short lived radionuclides produced at cyclotrons are generally limited to about 400 GBq.

The great advantage of a cyclotron is that short-lived β^+-emitting radionuclides of biological elements like carbon, nitrogen, oxygen and fluorine can be easily produced. They are of particular interest in the study of organ physiological functions using PET. The new approach to utilize metal complexes in diagnostic studies is also realized by using *non standard positron emitters*, that is, positron-emitting radionuclides of metals, which are produced at cyclotrons. Needless to say that, if proper precautions are undertaken, charged-particle induced reactions can lead to radioactive products of high specific activity. Although in reactor production as well, as discussed above, high specific activity product could be made available if use is made of a decay product rather than of the parent itself (e.g., ^{99m}Tc obtained via the decay of ^{99}Mo), in general the specific activity remains a problem. Furthermore, no suitable reactor-produced radionuclide of the above mentioned biological elements is available for in vivo diagnostic investigations.

Shift in Production Technologies

The production technologies of medical radionuclides are constantly under investigation because new demands keep on emerging. Those demands are mostly related to one or all of the following factors: increase in production yield, higher purity, higher specific activity and security in supply. The existing or developing technologies thus often require a shift to newer technologies, either using a different procedure at the same irradiation facility or making resort to a complementary facility. More discussion on this topic will follow in the later part of this book.

1.3.4 Generator Produced Radionuclides

Several medical radionuclides are not produced directly through a nuclear reaction. Instead they are obtained as decay products of their parents. Those products are called

generator produced radionuclides. Generally the parent radionuclide is adsorbed on a column and the daughter is eluted periodically (but other systems are also possible).

The general principle of a generator is that the half-life of the parent is longer than that of the daughter. This leads to a transient decay equilibrium within a reasonable time and the number of nuclei of the daughter (N_2) at time t can be calculated by the equation:

$$N_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} \times N_1^0 \; e^{-\lambda_1 t}$$

where $N_1{}^0$ is the initial number of nuclei of the parent, and λ_1 and λ_2 are the decay constants of the parent and the daughter, respectively. In terms of radioactivity, at equilibrium the ratio of the daughter activity to the parent activity (A_2/A_1) is higher than the parent activity by the factor $\lambda_2/(\lambda_2-\lambda_1)$. An example of such a generator system is ^{99}Mo (2.75 d)/^{99m}Tc (6.0 h) where $\lambda_1 < \lambda_2$. However, if the half-life of the parent is much longer than that of the daughter ($\lambda_1 \ll \lambda_2$), then a secular equilibrium is reached and the above equation is reduced to $N_2 = N_1 \frac{\lambda_1}{\lambda_2}$. In this equilibrium, the daughter activity will not exceed the parent activity, that is, $A_1 = A_2$. An example is the ^{68}Ge (271.0 d)/^{68}Ga (1.15 h) system.

Four widely used generator systems are ^{68}Ge/^{68}Ga, ^{82}Sr/^{82}Rb, ^{90}Sr/^{90}Y and ^{99}Mo/^{99m}Tc. It is emphasized that in a generator system several sequential separations should be possible and the daughter activity should have a high value over a relatively long time. In certain decay systems where the parent and the daughter have almost comparable half-lives, or when the parent is even shorter lived than the daughter, the separation of the daughter is meaningful only once because of the drastic decrease in its activity in the second or third separation cycle. Such a parent–daughter system has to be denoted as a *precursor system*, and not a generator system. Two prominent examples are $^{124}\mathrm{Xe}(\mathrm{n},\gamma)^{125}\mathrm{Xe} \xrightarrow{EC} {}^{125}\mathrm{I}$ and $^{130}\mathrm{Te}(\mathrm{n},\gamma)^{130\mathrm{m,g}}\mathrm{Te} \xrightarrow{\beta^-} {}^{131}\mathrm{I}$, where the desired daughter radionuclide is separated after the complete decay of the parent. To call such a system as "generator" is a misnomer.

It is worth pointing out that the parent nuclide of a generator may be produced in a reactor or at a cyclotron. In the above mentioned four cases, for example, ^{99}Mo and ^{90}Sr are produced using a reactor and ^{68}Ge and ^{82}Sr at a cyclotron. Detailed discussions of the production methodologies involved are given in later sections of this book.

1.4 Development of Novel Medical Radionuclides

The development of a novel radionuclide for medical application calls upon interdisciplinary work in several directions. It involves the so-called *four pillars*, namely, studies related to nuclear data, development of irradiation technology,

elaboration of chemical separation scheme and establishing quality assurance. Most of the development work is presently related to cyclotron production of radionuclides, but some work on the improvement of reactor radionuclides is also continuing. There are many similarities in the development of radionuclides using a reactor or a cyclotron, as far as chemical processing and quality control methods are concerned. With regard to nuclear data and irradiation technology, however, the cyclotron production of a radionuclide is much more demanding than that using a reactor.

The aim of accurate knowledge of nuclear data is to facilitate the choice of a radionuclide for a particular application and to provide optimum conditions for its production with high purity. Thus, the nuclear data provide the scientific basis for a new production route. The development of high-current targetry allows to produce the radionuclide in quantities sufficient for applications and the chemical processing renders the radioactive product in a suitable form for internal medical use. All those aspects need detailed consideration.

1.5 Scope of this Book

This book aims at presenting a clear understanding of the science and technology involved in the production of medical radionuclides at reactors and cyclotrons. The basic approach is to describe the principles and methodologies in a generally understandable way rather than indulging in the intricate technical details of a production process.

To this end, the three major production parameters, namely, nuclear data, targetry for high-current irradiations and chemical processing, are treated in detail in three separate chapters. Closely connected with chemical processing is the quality assurance of the radionuclide produced. It is also explicitly discussed. Thereafter, consideration is given to the production methodologies of the well-established standard radionuclides used in patient care (both diagnosis via SPECT and PET, and internal radionuclide therapy). The major emphasis in this book is, however, on the development of novel metallic radionuclides, especially utilizing cyclotrons. Among those radionuclides are *non-standard positron emitters*, which are finding increasing applications in PET to study slow metabolic processes, and *radionuclides for targeted therapy*, which emit low-energy β^- and α-particles or conversion and Auger electrons. The development and production work related to those radionuclides is treated in a separate chapter in somewhat more detail. The development and medical application of novel metallic radionuclides is progressing at a tremendous pace. For several new applications, further novel radionuclides need to be developed. Attempts are also underway to utilize new irradiation facilities for radionuclide production purposes. All those new perspectives are briefly considered in the last chapter of the book.

Furthermore, for following some of the development work over the last 35 years, seven review articles, periodically published by the author, are given as appendices to the main body of this book. They deal with the following:

- Nuclear data relevant to cyclotron-produced radionuclides (Appendix I); RCA **30**, 147–162 (1982).
- Production of radiohalogens (Appendix II); RCA **34**, 25–40 (1983).
- Cyclotron production of generator radionuclides (Appendix III); RCA **41**, 111–117 (1987).
- Therapeutic radionuclides and nuclear data (Appendix IV); RCA **89**, 297–302 (2001).
- Development of novel positron emitters (Appendix V); RCA **99**, 611–625 (2011).
- The present and future of medical radionuclide production (Appendix VI); RCA **100**, 635–651 (2012).
- New trends in nuclear data research (Appendix VII); RCA **101**, 473–480 (2013).

It is hoped that this book presents a balanced view of the science and technology involved in the production and development of medical radionuclides, and that it will attract the attention of graduate students, researchers and others interested in this field.

2 Nuclear Data

2.1 General

The term nuclear data encompasses all data which describe either the properties of nuclei or their interactions. In literature a huge body of data is available which, in general, can be grouped under three headings, namely, nuclear structure, nuclear decay and nuclear reaction data (Fig. 2.1). The nuclear structure data are related to configuration of nucleons within a nucleus at rest or in an excited state, depicted in the form of nuclear levels. At low excitation energies *discrete levels* occur, each level being characterised by its spin, parity and gamma transition probability. At high excitation energies, the levels become indistinguishable and they are collectively called the *continuum* region. The nuclear decay data refer to decay properties of radioactive nuclei and include parameters such as half-life, energies and intensities of emitted radiation as well as their sequences of emission and correlations. The nuclear reaction data describe the interaction of two nuclei, the important parameters being *Q*-value, cross section of the reaction, energy and angular distribution of the emitted particle, yield of the reaction product and so on.

The major aims of nuclear data research are:

a) to test nuclear models and thereby to advance nuclear theory,
b) to provide reliable data for applications in various fields.

Continuous work has been going on for the last 80 years to improve our knowledge of nuclear properties, and further studies are expected to continue also in the future. The provision of accurate experimental data helps to confirm and substantiate various nuclear models and theories. The major direction in nuclear data research today, however, is oriented towards applications. It is a well-organised field. Whereas measurements are done in a large number of laboratories around the world, the coordination of many activities, for example, compilation of data files and libraries, and dissemination of data, is generally done by four major regional data centres, namely National Nuclear Data Centre, Brookhaven (USA), Data Bank of the Nuclear Energy Agency, Paris (France), Nuclear Data Section of the International Atomic Energy Agency (IAEA), Vienna (Austria) and Data Centre, Obninsk (Russia). Some of the large data files issued by them are EXFOR, ENSDF, ENDF-B/VIII.1, JEFF-3.2 and ROSFOND-2010.

Accurate nuclear data are needed for applications in energy-related research (fission, fusion, accelerated-driven systems, etc.) as well as non-energy-related studies (medical radionuclide development, radiation therapy, astrophysics, etc.). The scope of this chapter is limited to data for medical applications of radionuclides. The basic aim of the related data is to provide a fundamental base for

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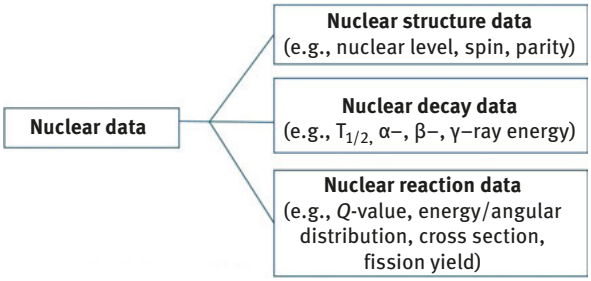

Fig. 2.1: Classification of nuclear data.

optimum production and internal application of those radionuclides. The activities consist of new experimental measurements, nuclear model calculations, and standardisation and evaluation of existing data.

As it has been mentioned in Chapter 1, the decay data of a radionuclide play a key role in its selection for internal medical use (diagnosis or therapy). The nuclear reaction cross-section data, on the other hand, facilitate its efficient production at a reactor or a cyclotron in high purity and sufficient quantity for application. The nuclear structure data have been gaining more significance in recent years because several of the nuclear isomeric states, decaying by emission of conversion or Auger electrons, are increasingly being used in some special therapeutic applications. A discussion of the various types of data involved is given below, with particular emphasis on charged-particle induced reaction cross-section data for production purposes.

2.2 Radioactive Decay and Nuclear Structure Data

Extensive efforts have been underway for more than 50 years on experimental determination, compilation and evaluation of decay data for a large number of radionuclides in general [24], and for about 200 radionuclides of medical interest in particular [23]. The basic decay schemes of the standard diagnostic and therapeutic radionuclides are known except for some special details in a few cases. As examples, decay schemes of three commonly used radionuclides, namely ^{99m}Tc in SPECT, ^{18}F in PET and ^{131}I in internal radiotherapy, are shown in simplified forms in Fig. 2.2(A)–(C), respectively. The radionuclide ^{99m}Tc ($T_{½}$ = 6.0 h); excitation energy: 143 keV deexcites via internal transition to 0.2 ns intermediate level which then further deexcites to the long-lived ground state and emits a main γ-ray of energy 141 keV (87.6%). This is ideal for SPECT studies. The dose to the patient is small. The radionuclide ^{18}F ($T_{½}$ = 109.8 min) decays simply to the ground state of stable ^{18}O via β^+ emission (97%) and electron capture (EC) (3%). It is ideally suited for PET investigations.

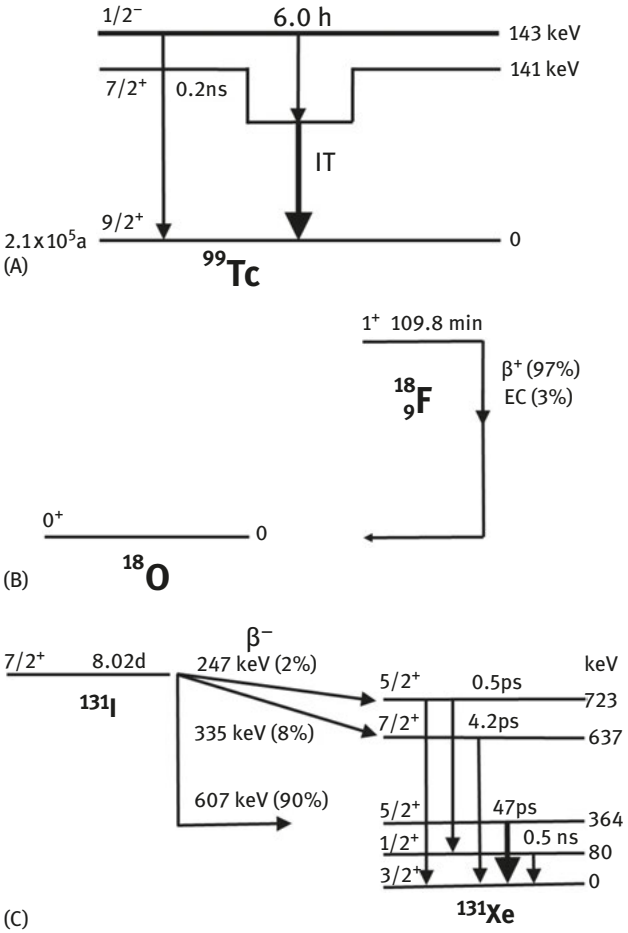

Fig. 2.2: Simplified decay schemes of (A) SPECT radionuclide ^{99m}Tc, (B) PET radionuclide ^{18}F and (C) therapy radionuclide ^{131}I.

In contrast to the above diagnostic radionuclides, ^{131}I ($T_{½}$ = 8.02 d) decays by several β^- transitions, the most prominent being the 607 keV transition (90%). The levels of ^{131}Xe populated in the decay of ^{131}I are shown. They are very short-lived and deexcite by γ-ray emission. The most intense 364 keV γ-ray is shown as a bold line. Since a lot of corpuscular radiation is emitted and the effective half-life of ^{131}I (especially in the thyroid) is also relatively long, the radiation dose involved is rather high. This radionuclide is therefore extensively used in internal radionuclide therapy.

Although the basic decay features of the standard radionuclides are well established, there is always room for improvement. New evaluations of many of the decay mass chains have been recommended by several working groups and, in

recent years, even some new experimental measurements have been initiated to clarify small discrepancies or to get more detailed knowledge on the relevant decay scheme (cf. for example a recent study on ^{82}Rb [35]).

As regards novel radionuclides, the decay data are fairly well established in many cases, but more efforts are still required to improve them [36] for several radionuclides. The decay data for many non-standard positron emitters, for example, need revision. In particular, the positron emission intensities should be determined with more modern techniques. In older measurements, many of the radioactive samples were prepared without radiochemical separations; they were radionuclidically not pure. Furthermore, β-ray spectroscopy has not attained the same precision as high-resolution γ-ray spectroscopy. The X-ray component, which is related to EC decay, was determined in older works generally using a gas counter. The modern methodology of determination of positron emission intensity consists of preparation of a very clean thin source, accurate measurement of the annihilation radiation (using both HPGe detector γ-ray spectroscopy and $\gamma\gamma$-coincidence counting) and determination of the EC component via high-resolution X-ray spectroscopy using a thin Si(Li) detector. The results for ^{64}Cu, taken from [37], are given in Fig. 2.3 as a typical example. The β^- branching was determined by mass spectrometry, and the contributions of EC and β^+ decay via the method described above. For most of the positron emitters rather away from the stability line, the β^- decay component is not observed and only EC and β^+ decay are in competition. New precise measurements are considered to be absolutely necessary to determine the positron emission intensities of the novel positron emitters. Also the intensities of the weak γ-rays need to be measured accurately, especially if they are used in cross-section measurement. In the above example, the intensity of the 1346 keV γ-ray is still controversial.

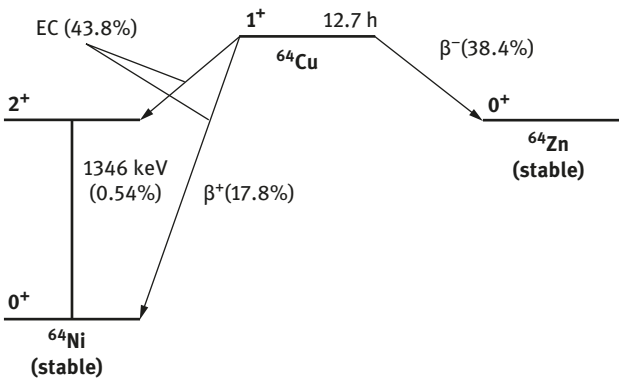

Fig. 2.3: Decay scheme of ^{64}Cu with intensities of emitted radiations, taken from Qaim et al. [37], with courtesy of De Gruyter.

Similar to non-standard positron emitters, for several novel therapeutic radionuclides as well, especially those emitting low-energy β^- or α-particles and conversion electrons, the intensities and spectra need better characterisation. This applies, for example, to ^{149}Tb which decays by a combination of EC, β^+ and α-particle emission. In the case of ^{103}Pd, the X-ray emission intensity is somewhat discrepant. The radionuclides ^{193m}Pt and ^{195m}Pt are very interesting isomeric states. They are very promising for Auger therapy and demand more precise determination of Auger electron spectra.

The above discussion simply outlines the general aspects of decay data of radionuclides. The main decay data of the standard medical radionuclides have been given in Table 1.1 and those of the novel radionuclides, considered later in this book, are given in chapters on production technology, where the production yields are also given.

2.3 Cross-Section Data of Neutron Induced Reactions

Neutrons have no charge, so they can easily penetrate various materials and induce radioactivity even at very low kinetic energies. With the increasing energy of the neutron, the list of competing reactions increases. Extensive experimental, theoretical and evaluation studies have been underway for many decades. The major aim was to supply accurate data for energy-related applications, but the radionuclide production technology has also greatly profitted from those data. It is to be emphasized that cross-section measurements of neutron induced reactions require special considerations. Using the four quasi-monoenergetic neutron sources, namely ^{7}Li(p,n)^{7}Be, ^{3}H(p,n)^{3}He, ^{2}H(d,n)^{3}He and ^{3}H(d,n)^{4}He, covering the energy region from about 0.2 to 20 MeV, measurements of excitation functions for the formation of many radioactive products have been performed. However, in the case of spectral neutrons, which are more commonly encountered and used in radionuclide production because of high fluxes (e.g., in a reactor), use of choppers, absorbers and time-of-flight (TOF) techniques is common to measure the cross sections. Those measurements are rather demanding. Nonetheless, a huge body of data has been accumulated and evaluated. The nuclear processes used in production of radionuclides in a nuclear reactor are discussed below.

2.3.1 Neutron Capture

This is the major activation reaction in a nuclear reactor and many radionuclides are produced via this route. Extensive measurements, compilations and evaluations on capture cross sections exist [38]. The direct capture of a neutron occasionally follows a sequential capture of another neutron. The two modes are discussed here.

Direct Capture

The (n,γ) reaction has generally a high cross section and therefore the yield of the product is also rather high. The excitation function of a typical neutron capture reaction [39] is shown in Fig. 2.4. Starting from the lowest energies (cold neutrons) and proceeding to about 1 eV, the cross section shows a $1/v$ dependence, that is, the cross section decreases inversely with the increasing kinetic energy of the neutron. The major interest is in the thermal energy region where the (n,γ) cross section is high and the neutron flux in a reactor is also high (see Fig. 1.1(B)). The energy spread of the neutrons in the thermal region is described by the well-known Maxwellian distribution, with maximum intensity at about 0.025 eV. In the epithermal region, the cross section has a resonance character and the integrated cross section (resonance integral) has a high value but, since the neutron flux is relatively low, the contribution of this region to the formation of the radionuclide is rather small. The high energy component of the neutron spectrum contributes only negligibly to the formation of the (n,γ) reaction product since both the spectrum-averaged reaction cross section and the neutron flux have low values. The curve for the ^{98}Mo(n,γ)^{99}Mo reaction taken from [39] and shown in Fig. 2.4 is based on a large number of experimental data points and extensive theoretical calculations. The

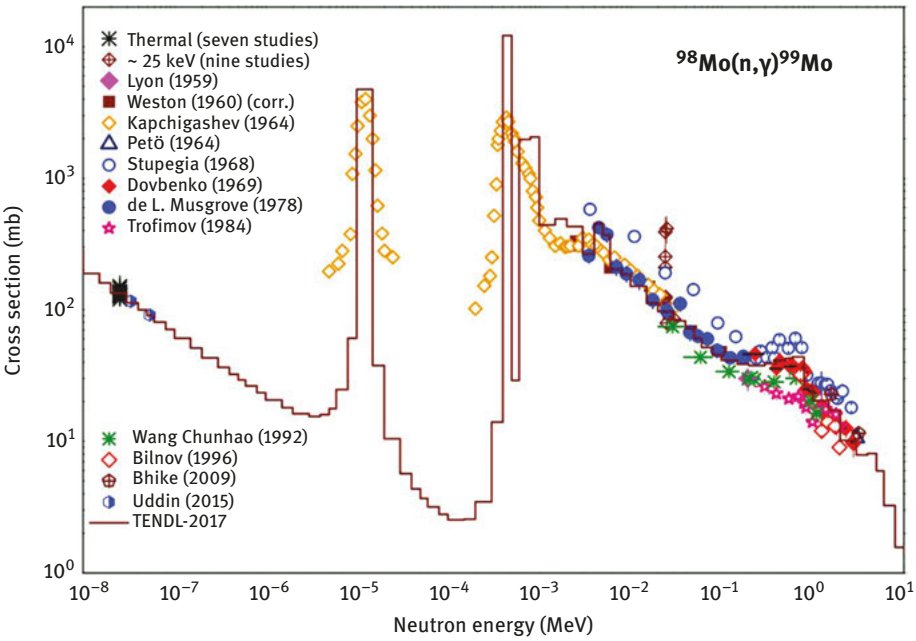

Fig. 2.4: Experimental data for the ^{98}Mo(n,γ)^{99}Mo reaction available in the literature together with the evaluated data given in the file TENDL-2017, taken from Tárkányi et al. [39], with courtesy of Springer.

recommended value of the (n,γ) reaction cross section for thermal neutrons is 0.130 ± 0.006 b and the resonance integral (I_0) amounts to 6.9 ± 0.3 b [38]. The (n,γ) cross section averaged over the fast neutron spectrum is estimated to be 14 ± 3 mb. Several other evaluations of the ^{98}Mo(n,γ)^{99}Mo excitation function have also been reported (cf. ENDF/B-VIII.1, JEFF-3.2). They generally agree with the accepted data for the production of ^{99}Mo.

It is evident that for calculating the activity of ^{99}Mo, a cross-section value of the (n,γ) reaction averaged over the whole reactor neutron spectrum cannot be used. Such a calculation should consider the three energy regions (thermal, epithermal and fast) separately. Thus if the activation of ^{98}Mo in a medium power reactor is calculated using the typical neutron flux density distribution for the DIDO reactor given in Table 1.2 and the cross-section data mentioned above, it is found that about 60% of the product ^{99}Mo activity is formed through the thermal neutrons and the rest through higher energy neutrons. This is a somewhat unfavourable case because here the σ_{th} is relatively low. In many other cases, for example in the reaction ^{152}Sm(n,γ)^{153}Sm, where σ_{th} is high, the contribution of the thermal neutrons to the product formation amounts to about 84%. The general experience is that the thermal component of the neutron spectrum plays a dominant role in the production of a radionuclide via the (n,γ) process. However, while calculating the production yield of the radionuclide, the contribution of both the thermal and the epithermal components of the neutron spectrum should be taken into account. It should also be mentioned that, while irradiating a sample in the core of a reactor, several threshold reaction products with relatively long half-lives may also be formed as impurities. For example, in irradiation of ^{nat}Mo, ^{92m}Nb ($T_{½}$ = 10.1 d), ^{95}Nb ($T_{½}$ = 35.0 d) and ^{95}Zr ($T_{½}$ = 64.0 d) are also formed via the ^{92}Mo(n,p)^{92m}Nb, ^{95}Mo(n,p)^{95}Nb and ^{98}Mo(n,α)^{95}Zr reactions, respectively [40]. At a few reactors, therefore, irradiations for radionuclide production are done in pure thermal columns. In general, however, a knowledge of cross sections of all possible reactions is important.

Sequential Capture

Occasionally, the radioactive product of an (n,γ) reaction not only shows radioactive decay but has also a tendency to capture another neutron. Thus the two processes, namely radioactive decay and sequential neutron capture, compete with each other. On the other hand, since the amount of the radioactive product is very small, the second neutron capture occurs mostly in high flux reactors. Furthermore, since the amount of the product of the (n,γ) reaction increases with time, the extent of sequential capture also increases with time. The build up of the final product can be calculated through a set of Bateman equations, but the calculation is only approximate. As regards the determination of nuclear data for the second stage of production, it is obvious that the difficulties are tremendous

due to the very small number of target nuclei involved. Nonetheless, attempts have been made in a few important cases to obtain some data both on thermal neutron capture cross sections and resonance integrals. The two most important examples are ^{164}Dy(n,γ)^{165}Dy(n,γ)^{166}Dy and ^{186}W(n,γ)^{187}W(n,γ)^{188}W. In the first case, the product activity ^{165}Dy decays with a half-life of 2.35 h but has also a very high (n,γ) capture cross section (σ_{th} = 3500 b). The product ^{166}Dy decays with a half-life of 81.5 h to the daughter ^{166}Ho ($T_{1/2}$ = 26.8 h), which emits low energy β^- particles. Since the final product is in no-carrier-added form, it has a high specific activity and is suitable for internal radiotherapy. The same applies to the second case as well. The product of the ^{186}W(n,γ)^{187}W reaction decays with a half-life of 23.7 h but the cross section of the process ^{187}W(n,γ)^{188}W (σ_{th} = 70 b) is relatively high and so the product ^{188}W is formed in sufficient quantity. Because of its relatively long half-life, the final product ^{188}W is used in the preparation of the generator system ^{188}W (69.0 d)/^{188}Re (17.0 h). The no-carrier-added daughter product finds application in internal radiotherapy.

A yet another case of sequential capture of the neutron entails the capture not by the radioactive product of the (n,γ) reaction but by the decay product of the (n,γ) reaction product. The most typical example is the formation of the very important radionuclide ^{125}I. It is produced via the $^{124}\mathrm{Xe}(\mathrm{n},\gamma)^{125}\mathrm{Xe} \xrightarrow{EC} {}^{125}\mathrm{I}$ process. During the irradiation of the ^{124}Xe gas, the (n,γ) reaction product ^{125}Xe decays with a half-life of 16.9 h to the long-lived ^{125}I ($T_{1/2}$ = 59.4 d), which gets accumulated in the irradiation vessel. In case of a short irradiation, pure ^{125}I can be separated from the vessel. However, if the irradiation is long, and enough ^{125}I nuclei have been accumulated, due to the relatively high cross section of the ^{125}I(n,γ)^{126}I process (σ_{th} = 900 b), the amount of ^{126}I formed is not negligible. This then becomes an undesired impurity. A knowledge of nuclear data therefore helps to choose a suitable irradiation time to keep the impurity level to a minimum.

2.3.2 Neutron Induced Fission

The splitting up of a nucleus under the impact of an incident neutron into two unequal or equal parts is termed as fission, the former being called *asymmetric* and the latter *symmetric* fission. With the increasing energy of the neutron the asymmetry decreases. Extensive experimental and theoretical studies have been performed to understand the phenomenon of fission. In general, up to 200 different radionuclides are formed in the fission process. Their nuclear data are of great importance in nuclear technology. From the viewpoint of radionuclide production, however, the most relevant nuclear data are the fission yields of the products. In low-energy fission, the mass distribution curve of the products shows a two hump structure separated by a deep valley. The mass chain fission yields have been generally accurately measured and thoroughly evaluated.

It is understood that the radionuclide production via the fission process is meaningful only for products of relatively high yields, that is, the products that lie on one or the other hump of the mass distribution curve. Those humps relate to nuclides with masses in the range of 85–106 and 129–140. Some of the long-lived products with their respective fission yields are listed in Table 2.1. The very long-lived products ^{99}Tc, ^{129}I and ^{135}Cs are a menace in the disposal of radioactive waste from nuclear power reactors. The radioactive ^{137}Cs is partly used in external radiation therapy. The radionuclide ^{89}Sr is commonly used in internal radiotherapy but it cannot be obtained in a pure form via the fission process because it is always contaminated with ^{90}Sr. Its preferred production route is therefore the ^{89}Y(n,p)^{89}Sr reaction (see below). The emphasis in radionuclide production via the fission process is thus limited to ^{90}Sr, ^{99}Mo and ^{131}I.

Table 2.1: Some long-lived radionuclides formed in high yields in the thermal neutron induced fission of ^{235}U.

Radionuclide	Half-life	Fission yield (%)
^{89}Sr	50.5 d	4.69 ± 0.06[a]
^{90}Sr	28.9 a	5.77 ± 0.40[b]
^{99}Mo	2.75 d	6.13 ± 0.09[a]
^{99}Tc	2.1×10^5 a	6.13 ± 0.09[a]
^{129}I	1.6×10^7 a	0.71 ± 0.03[a]
^{131}I	8.02 d	2.88 = ±0.26[b]
^{135}Cs	2×10^6 a	6.62 ± 0.23[a]
^{137}Cs	30.2 a	6.21 ± 0.45[b]

[a] From IAEA-INDC(NDS)-0534 (2008).
[b] From IAEA-Technical Report-473 (2011).

It should be emphasised that very elaborate chemical separation methods need to be applied to obtain the desired radionuclide in a radionuclidically pure form. However, the product is no-carrier-added, so its specific activity is high. The radiochemically separated ^{90}Sr is used to prepare the ^{90}Sr/^{90}Y generator. The isolated daughter ^{90}Y ($T_{½}$ = 2.7 d) is used in internal radiotherapy. Similarly the separated ^{99}Mo is utilized in the preparation of the ^{99}Mo/^{99m}Tc generator where the daughter ^{99m}Tc ($T_{½}$ = 6.0 h) finds application in SPECT. The radionuclide ^{131}I ($T_{½}$ = 8.02 d), on the other hand, is used directly in internal radiotherapy.

2.3.3 Neutron-Induced Charged-Particle Emission Reactions

The interaction of a neutron with a target nucleus may also lead to emission of a charged particle, especially in the region of light mass elements. The light mass

nuclei ^{3}He and ^{6}Li, for example, interact with thermal neutrons to produce a lot of tritium via the reactions ^{3}He(n,p)^{3}H (σ = 5330 b) and ^{6}Li(n,α)^{3}H (σ = 940 b). In general, however, the emission of a charged particle involves overcoming a certain barrier which consists of a sum of the energy threshold and the Coulomb barrier. The energy threshold is the minimum kinetic energy of the neutron needed to induce a reaction. The Coulomb barrier on the other hand may, in certain cases, be relaxed through the tunneling effect, that is, sub-Coulomb barrier emission may occur. The emission of a proton has generally a higher probability than the emission of an α-particle; so the (n,p) reaction is often utilized in medical radionuclide production in a reactor. It should, however, be kept in mind that the fission neutron spectrum has only a small fraction of neutrons in the MeV region (cf. Fig. 1.1(B)). The (n,p) reaction cross section with fission neutrons is thus generally low. There are two methodologies for obtaining the (n,p) reaction cross section averaged over the fission neutron spectrum:

a) Direct measurement of the yield of the radioactive product after irradiation of the target with a given fast neutron flux. The result describes the *integral cross section*.
b) Measurement of the excitation function of the (n,p) reaction using quasi-monoenergetic neutron sources covering the energy range up to about 20 MeV. The cross section is then averaged over the fission neutron spectrum. It is then called *integrated cross section*.

A comparison of the integral and integrated cross section serves to validate the two types of data. Measurement of an excitation function often delivers good information on the mechanism of emission of the charged particle, but the integrated data have generally higher uncertainties than the integrally determined values.

The excitation function of the ^{32}S(n,p)^{32}P reaction, taken from [41], is shown in Fig. 2.5 as an example. A large number of measurements were done and the results showed considerable discrepancies. The two curves given in Fig. 2.5 are based on rigorous evaluations of all data. The dumb-bell-shaped curve is typical of the excitation function of an (n,p) reaction. A few fluctuations (or resonances) in the energy region up to 5 MeV are characteristic of light mass target nuclei because of preferential population of some of the discrete energy levels of the product nucleus. The cross section averaged from this excitation function over the fission neutron spectrum amounts to 68.2 mb. Several integral measurements of the cross section of the same reaction using the fission neutron spectrum gave a mean value of 69.0 ± 1.4 mb [41, 42]. The agreement is excellent but the effort devoted to data evaluation has been extensive, partly because of the importance of this reaction in reactor dosimetry (cf. IAEA-IRDFF -2014). Incidentally, this reaction was the original process used by Chievitz and Hevesy [6] to produce ^{32}P using neutrons from a Ra–Be source (see Section 1.1).

Besides ^{32}P, several other medically useful radionuclides have been produced via the (n,p) reaction. The common examples are ^{35}Cl(n,p)^{35}S ($T_{½}$ = 87.5 d), ^{64}Zn(n,p)^{64}Cu

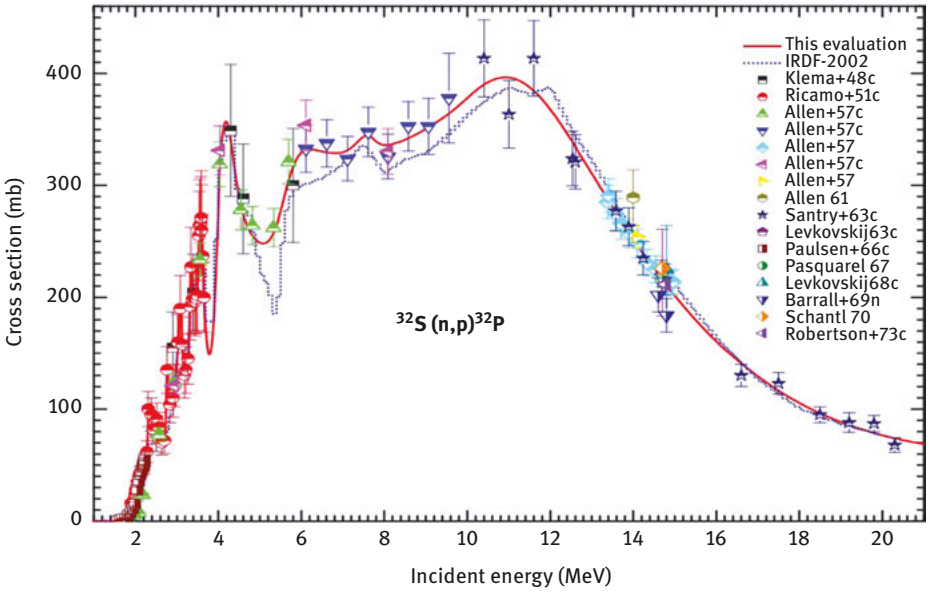

Fig. 2.5: Excitation function of the $^{32}S(n,p)^{32}P$ reaction, taken from Qaim et al. [41], with courtesy of IAEA.

($T_{½}$ = 12.7 h), $^{67}Zn(n,p)^{67}Cu$ ($T_{½}$ = 2.58 d) and $^{89}Y(n,p)^{89}Sr$ ($T_{½}$ = 50.5 d). The fission neutron spectrum averaged cross sections of all those reactions have been extensively measured and evaluated, and recommended data are available [41, 42]. The excitation function measurements of those reactions up to 20 MeV, however, are far from being complete and therefore the neutron spectrum integrated cross sections of those reactions often show discrepancies with the integral measurements [36]. Nonetheless, for production purposes the integral database is reliable. The yields are low because the cross sections are rather small. The batch yields achieved after long reactor irradiations are, however, generally enough for medical applications. The major advantage of the (n,p) process is that the product radionuclide is obtained in a no-carrier-added form.

In addition to routine production of the above mentioned radionuclides, the (n,p) process has been investigated for the production of several other radionuclides as well. Some of the examples are $^{90}Zr(n,p)^{90}Y$ ($T_{½}$ = 2.7 d), $^{153}Eu(n,p)^{153}Sm$ ($T_{½}$ = 1.93 d), $^{169}Tm(n,p)^{169}Er$ ($T_{½}$ = 9.4 d) and $^{175}Lu(n,p)^{175}Yb$ ($T_{½}$ = 4.2 d). The work has, however, been limited to cross-section measurement [43]. Due to the rapidly decreasing value of the (n,p) reaction cross section with the increasing mass of the target nucleus, no radionuclide beyond mass 90 is produced via the (n,p) reaction.

It should be observed that out of the above-mentioned five radionuclides produced via the (n,p) reaction, viz. ^{32}P, ^{35}S, ^{64}Cu, ^{67}Cu and ^{89}Sr, the production of

^{64}Cu and ^{67}Cu has shifted mainly to cyclotron but the other three are still produced via the (n,p) reaction in nuclear reactors.

2.4 Charged-Particle Induced Reaction Cross-Section Data

2.4.1 General

In contrast to neutron induced reaction cross sections, which received great attention right from the beginning because of their energy-related applications, the charged-particle induced reaction cross sections were initially measured mostly in the context of reaction mechanisms. The main emphasis in those investigations was on the measurement of emitted particles, especially their energy and angular distributions. In principle, an integration of the emitted particle spectrum over the whole range of energy and angular distribution would yield the cross section for the formation of a product nucleus. In practice, however, such fundamental studies on nuclear reactions hardly reported integrated cross sections for the formation of product nuclei. Though some attempts to determine the formation cross sections of the medically important radionuclides ^{11}C, ^{13}N and ^{18}F via measurements of the neutron spectra emitted in (p,n) reactions on ^{11}B, ^{13}C and ^{18}O, respectively, were fairly successful [44], the integral cross-section data as a function of incident particle energy (*excitation function*), needed in radionuclide production, required special consideration. Experimental work specifically related to cyclotron production of individual radionuclides was started already in the late 1960s and continued in 1970s in several laboratories, for example, Brookhaven, London, Saitama and Jülich. But more systematic and critical studies on the role and status of charged-particle induced reaction cross-section data relevant to the production of medical radionuclides were initiated at the Forschungszentrum Jülich in the late 1970s. After two plenary talks in 1978 at the newly established International Conferences on *Radiopharmaceutical Chemistry* in Oxford and *Nuclear Data for Science and Technology* at Harwell, this author wrote the first review article on the topic in 1982 (see Appendix I), discussing various aspects of this emerging area of research. The field developed further and the data for the production of radiohalogens as well as generator parents at cyclotrons were also reviewed (Appendices II and III, respectively). Thereafter, the IAEA got interested in the subject and several consultants´ and technical meetings were held, all under guidance of this author. Those meetings led to the formation of several successive Co-ordinated Research Projects (CRPs) for standardisation of charged-particle data. Over the years it has become a still more interesting area. The field of charged-particle induced reaction cross-section data is still developing. Therefore, its salient features are discussed below in some detail.

2.4.2 Significance of Data

The significance of charged-particle data was discussed already in 1982 (see Appendix I); here a brief updated outline is given.

Reaction Cross Section

The cross-section data are needed in radionuclide production for

(i) determining the energy range optimum for the production of a specific radionuclide,
(ii) calculating the expected thick target yield of the radionuclide to be produced,
(iii) calculating the yields of radionuclidic impurities for a given thickness and enrichment of the target material.

A selection of the projectile energy range that will maximise the yield of the desired product and minimise that of the radioactive impurities is of vital importance in optimising a production method. At low projectile energies, the number of open reaction channels is generally small but with increasing incident particle energies several competing reactions set in. Whereas the non-isotopic impurities produced can be removed by chemical separations, the level of isotopic impurities can be suppressed only by using enriched isotopes as target materials and/or by careful selection of the particle energy range effective in the target. At high incident projectile energies, naturally the nuclear data needs are also higher. Often only a very narrowband of energy is utilized to ensure the purity of the desired radionuclide. A knowledge of the excitation function plays a very important role, especially in designing gas targets. The incident energy of the projectile, the length of the target as well as the pressure of the target gas are to be selected in such a way that only the desired portion of the excitation function is utilized, the remaining energy of the projectile being dumped on a beam-stop.

Thick Target Yield

The activation equation for the formation of a product via a charged-particle induced reaction using a very thin target given in Section "Some Special Considerations" in Chapter 1 is used in the following modified form while calculating the yield of a radionuclide from a target of a particular thickness (thick target yield):

$$A = \frac{N_L \cdot H}{M}\, I\, \left(1 - e^{-\lambda t}\right) \int_{E_1}^{E_2} \left(\frac{dE}{d(\rho x)}\right)^{-1} \sigma(E) dE$$

where N_L, H, M, I, λ and t have the same meaning as mentioned in Section "Some Special Considerations" in Chapter 1. The term $\left(\frac{dE}{d(\rho x)}\right)$ describes the stopping power, $\sigma(E)dE$ the cross section at energy E, and E_1 and E_2 are the lower and upper energy

limits of the projectile in the target. Yields are generally calculated for a certain energy range for a current of 1 μA and irradiation time of 1 h (MBq μAh^{-1}). In some cases, saturation yields appear to be more meaningful (MBq μA^{-1}).

The calculated yield value from the above equation represents the maximum yield, which can be expected for a given target system. In practice, however, the experimentally obtained yield in a high-current production run is invariably lower than the theoretical value, possibly due to inhomogeneity in the incident beam, radiation damage effect, loss of the product as a result of high power density effective at the target and so on. It is therefore emphasised that the result of an experimental thick target yield measurement is not enough for optimising a production process. The basic parameter in the production of a radionuclide is the cross section and not a particular target yield. The latter reflects only the specific conditions prevalent during the production process. An accurate knowledge of the excitation function, and therefrom the calculated thick target yield, helps in designing target systems capable of giving higher yields. On the other hand, it should also be pointed out that the problems associated with the large-scale production of radionuclides are not solved simply by measuring the cross section. Other factors like suitability of a material for target construction, heat transfer, remote handling, chemical processing and quality control are often of greater importance. The efforts in the field of nuclear data should therefore go hand in hand with the other development work.

Similar to the yield calculation for the desired radionuclide, the yields of the impurities can also be calculated if the excitation functions of the relevant reactions are known. It is then easy to keep a check on the radionuclidic impurities associated with a particular production method.

2.4.3 Experimental Determination of Charged-Particle Induced Reaction Cross Section

The experimental techniques involved in the determination of charged-particle induced reaction cross sections are somewhat different than those in the case of neutron induced reactions. As discussed in Section “Some Special Considerations” in Chapter 1, this is mainly due to the rapid decrease of the projectile energy in the target material and the accompanying change in the cross section. The experimental techniques were outlined earlier (see Appendix I). However, the cross-section measurement methodology has experienced a tremendous improvement in recent years. This warrants a more detailed discussion of this subject.

Two techniques have been used for measuring reaction cross sections. The first one is applicable in the case of variable energy cyclotrons. Thin samples of the target material are irradiated either with extracted beams of varying energies or at appropriate radii in the internal beam. The activated products are assayed quantitatively, often using radiochemical methods. The second technique consists of irradiating a set of foils, thin sandwiches or thin pellets of the material under investigation

together with a few monitor foils, placed together in a stack. The induced radioactivity in each foil is then determined. This technique is called *stacked-foil* technique. Besides foils the technique has also been applied to gas targets. Several thin-walled gas cylinders are placed in a row to constitute a stack of samples. A schematic arrangement for irradiation of a stack of foils is shown in Fig. 2.6(A) and that for irradiation of gas cylinders in Fig. 2.6(B). The monitor foils are used to determine the beam intensity and adjust the beam energy (see below).

The use of stacks of foils, pellets or cylinders is very useful since cross-section data at several energies are obtained in a single irradiation. On the other hand, if proper precautions are not taken, considerable errors may occur both in the energy scale and the cross section. Over the years, this technique has attained a great degree of sophistication in four directions, namely thin sample preparation, beam characterization, projectile energy adjustment in the stack and radioactivity measurement. A discussion of those features is given below.

Thin Sample Preparation and Irradiations

In order to avoid excessive energy degradation in each sample it is essential to use thin foils. This is all the more important in the low-energy rising part of the excitation curve to be able to get more detail. The foils should, however, be thick enough to produce measureable activities for getting good counting statistics. In the case of ductile metals (e.g., Al, Ti, Cu, Mo, Ag and Au), foils of varying thicknesses are commercially available. However, it is absolutely necessary to determine the thickness of each foil in the laboratory and not to rely simply on the supplier's specification. Most of the reaction cross-section measurements reported in the literature in recent years were carried out using foils of metals of natural isotopic composition. Thin foils of non metallic and amorphous substances, however, are difficult to get. Similarly the isotopically enriched target material is also generally supplied in powder form. Thus, in those cases special preparative methods are necessary.

The techniques of sublimation and vacuum evaporation have been occasionally used for getting thin films on a suitable backing [45]. The use of sedimentation process to prepare thin samples of isotopically enriched amorphous materials has found a relatively wide application [46, 47], although the spread is often not uniform. Occasionally, the target material in powder form was pressed to obtain a thin pellet [46]. A more elegant method is electrolytic deposition which gives rise to desired thin films which are uniform in thickness, dense and adherent. Uniformity in the thickness of the film is a very important parameter in cross-section work. Through the development of a small-volume electrolytic cell [48, 49], with a hanging rotating electrode in the middle, the technique was found to be very useful. A sketch of the apparatus is shown in Fig. 2.7. Using different electrolytic solutions, the apparatus has been extensively applied over the last 25 years at the Forschungszentrum Jülich to prepare thin samples (1–10 μm thickness) of Cr, Fe,

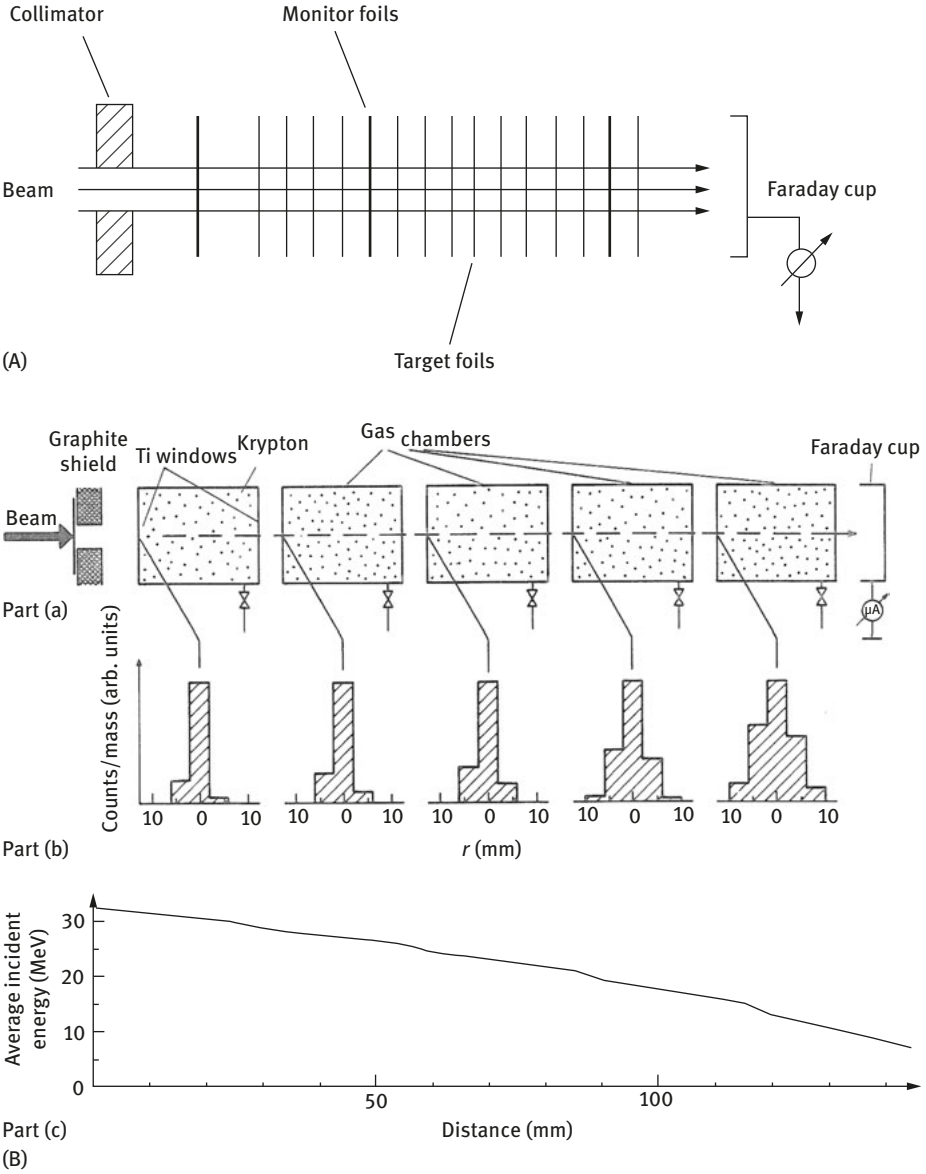

Fig. 2.6: Schematic arrangement for irradiation of samples with a charged particle beam: (A) stack of target and monitor foils, (B) Part (a) stack of gas cylinders, (b) broadening beam in rear cylinders, determined by the activity distribution in the front Ti window, (c) decreasing ^{3}He-particle beam energy in rear cylinders, calculated by the code STACK. Figure (B) is taken from Tárkányi et al. [57], with permission from Elsevier.

Ni, Zn, Se, Te and Os, often working with small amounts of rather expensive, highly enriched target isotopes (e.g., ^{50}Cr, ^{54}Fe,^{61}Ni, ^{64}Ni, ^{70}Zn, ^{76}Se, ^{120}Te, ^{123}Te, ^{124}Te,

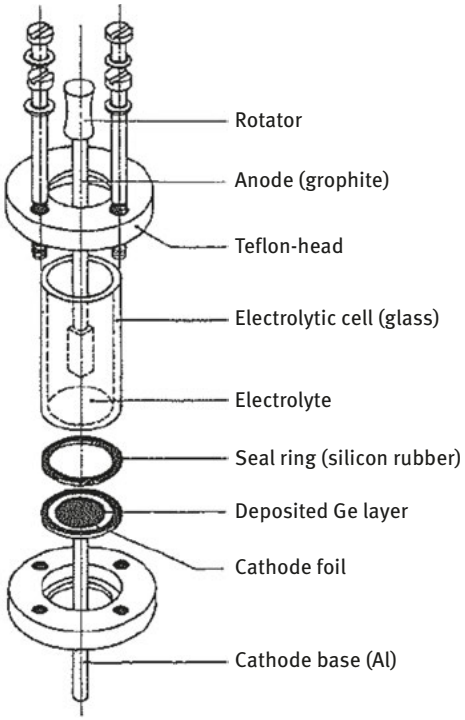

Fig. 2.7: Schematic diagram of the mini-cell used for electrolytic deposition of metals (e.g., ^{70}Ge from a solution of $^{70}GeCl_4$ in propylene glycol), taken from Mushtaq and Qaim [48], with courtesy of De Gruyter.

^{125}Te, ^{126}Te and ^{192}Os), to measure cross sections of proton, deuteron, ^{3}He- and α-particle induced reactions, especially in the low-energy region up to 25 MeV. After preparation, the thickness of each sample was accurately determined.

In addition to the thickness of the foil or of the deposited material, it is important to keep a check on the chemical purity of the prepared sample. It is therefore advisable to submit a few independent samples to full physicochemical analysis. Furthermore, if an enriched isotope is used as the target material, it is important to know not only the percentage enrichment of the target isotope but also the exact isotopic composition of the target since many of the radioactive impurities accompanying the desired radionuclide may originate through nuclear reactions on the less abundant isotopes in the target.

As far as gas targets for nuclear reaction cross-section measurements are concerned, useful cryogenic techniques have been developed for handling expensive isotopically enriched gases. A typical apparatus is shown in Fig. 2.8 [50]. It is made of stainless steel, with manually operated bellow valves and metal tube fittings. The connections between the gas cells and the movable gas handling system had to be frequently separated; therefore they consisted of O-ring face sealed couplings.

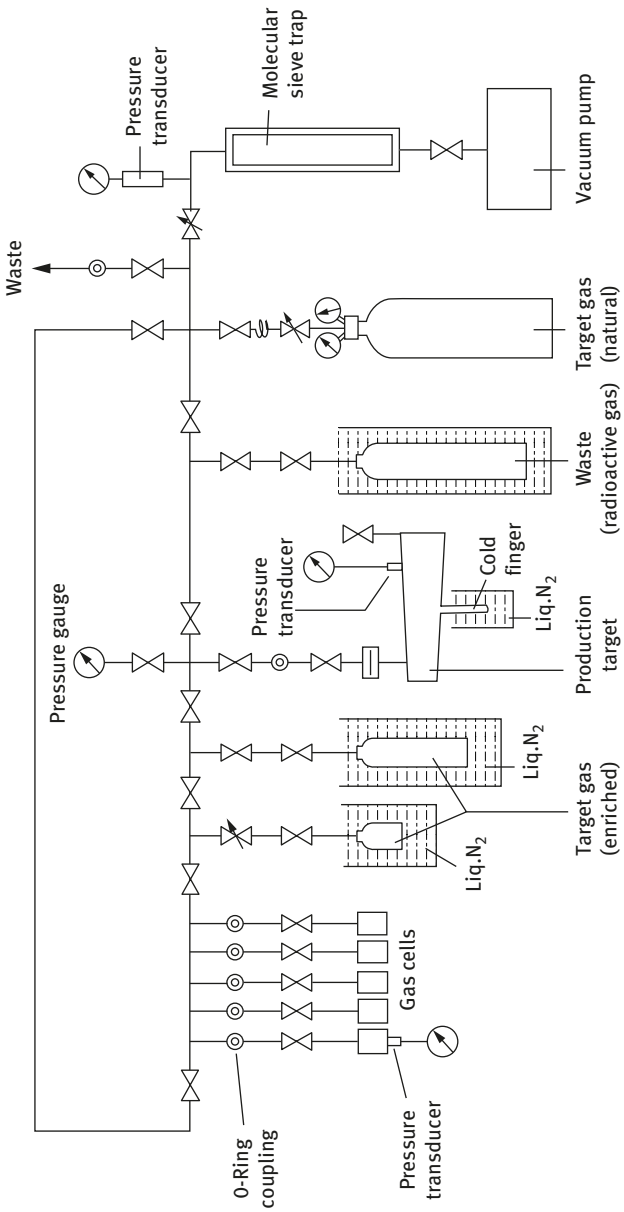

Fig. 2.8: Sketch of gas handling system for cross-section measurements on enriched gas samples. A production target could also be handled using the same apparatus, taken from Tárkányi et al. [50], with courtesy of De Gruyter.

Prior to use, the gas cells and the handling system were carefully checked against leakage at 10^{-6} Torr using a helium leak detector. The enriched target gas was generally delivered by the supplier under low pressure in a relatively large cylinder. It was therefore necessary to transfer it first by cryogenic pumping to a small 10 mL container. Thereafter, the gas cells used for cross-section measurements were filled to a pressure of 1–2 bar from that container. The same vacuum line could also be used for filling or evacuating a production target with enriched or natural gas. Similar to highly enriched solid targets, in recent years extensive cross-section measurements on isotopically enriched gases, like $^{18}O_2$, ^{38}Ar, $^{78,82,83}Kr$ and ^{124}Xe, were also performed at the Forschungszentrum Jülich.

Beam Characterisation

The charged-particle beam from an accelerator or a cyclotron needs to be properly characterised before it impinges on a target, the quality factors being the energy, the shape and the intensity. The energy of the extracted beam is generally given by the accelerating machine parameters and the shape of the beam is controlled, besides the magnets, by the collimator placed in front of the irradiation target. The intensity of the beam is registered by charge collection.

In general, small-sized linear accelerators (van de Graaff, pelletron, etc.) deliver more well-defined beams than a cyclotron. Regarding cyclotrons, the older physics machines delivered high-quality beams (e.g., at Berkeley, Brookhaven, Harwell, Birmingham, Amsterdam, Saclay, Jülich and Saitama) but of low intensities. A lot of work on nuclear reaction cross-section measurements was done using those cyclotrons. However, the production possibilities of radionuclides in quantities sufficient for medical applications were limited. With the development of application-oriented robust cyclotrons (levels II–IV, Table 1.3), the emphasis has now become more on higher intensity rather than on beam quality. Some of them have a short beamline for tuning an extracted beam while in many others the production target is directly connected to the exit port. In recent years, several of those dedicated cyclotrons have also found some application in nuclear reaction cross-section measurements. The characterisation of those beams is absolutely necessary. It is briefly described below.

a) Incident Particle Energy

The determination of the incident particle energy is particularly important in nuclear reaction cross-section measurement. This has been done by developing TOF methods [51, 52], but more commonly by the activation method [49] which involves a comparison of the normalised radioactivities of two different reaction products induced in a monitor foil. This method was used, for example, to determine energies of the extracted proton beams from two cyclotrons at Jülich, namely BC1710 and CV28. For this purpose a thin Cu foil (~20 μm thick) was placed in front of a target

and irradiated with protons. The radioactivities of the three products, viz. ^{62}Zn ($T_{½}$ = 9.2 h), ^{63}Zn ($T_{½}$ = 38.5 min) and ^{65}Zn ($T_{½}$ = 243.9 d), were determined by γ-ray spectrometry and normalised for the cross section and the irradiation-time dependent saturation factor. Therefrom the ratios of the activities of ^{63}Zn/^{62}Zn and ^{62}Zn/^{65}Zn were obtained. The ratios were also calculated theoretically from the evaluated excitation functions [53] of the three relevant reactions, namely ^{nat}Cu(p,x)^{62}Zn, ^{nat}Cu(p,x)^{63}Zn and ^{nat}Cu(p,x)^{65}Zn. From a comparison of the two ratios, the average energy of the proton beam within the foil was deduced. The energy of the extracted proton beam at the cyclotron BC1710 was found to be 16.7 MeV [54]. This value is about 3% lower than the value of 17.2 MeV given by the cyclotron parameters. Similarly the proton beam energy at the compact cyclotron CV28 was found to be 18.7 MeV [49], which was 6.5% lower in comparison to 20.0 MeV given by the cyclotron parameters. Interestingly, at that cyclotron the TOF measurement [51] showed the proton energy to be 18.8 MeV. Thus, the radioactivity comparison method appears to be quite reliable for the determination of incident projectile energy in various energy regions, provided suitable cross-section data for monitor reactions with different thresholds are available. In recent years, the knowledge on monitor reactions has considerably enhanced [55]. Because of its simplicity the technique is therefore now being used in many laboratories engaged in nuclear reaction cross-section measurements.

b) Beam Shape

The beam coming out of the cyclotron and passing through a beamline generally falls on a collimator whereby it is reshaped by the setting of the aperture of the collimator. To determine the beam profile at the target position, a metal foil, for example, Nb, is irradiated and the glow is registered with a camera [56]. A simpler method is to irradiate a Cu foil at a low current of 1 μA, and to determine the contour of the radioactive spot by instant imaging. At the cyclotron BC1710 mentioned above, for example, an 8 mm aperture collimator was used and the Cu foil was irradiated immediately behind the collimator. The beam was found to be dense and more or less of spherical shape with a diameter of about 8 mm [54]. Another foil irradiated at 630 mm away from the collimator, however, showed a diffused shape, though the major intensity appeared to be concentrated over an area of about 9 mm diameter. It is therefore recommended that the samples to be irradiated for nuclear reaction cross-section measurements are placed as near as possible to the back of the collimator and the diameter of the irradiation sample is comparable to that of the collimator.

It should also be pointed out that the shape registered at the first foil of a stack undergoes some change within the stack due to scattering effect. This small change in shape is not of any great consequence as long as the sample and the monitor are of the same size and shape. In a row of gas cylinders, however, the beam scattering effect is very pronounced and care has to be taken that the beam remains within

the cell even in the farthest cylinder [57]. Considerable errors in reaction cross sections would occur if part of the beam is lost within a cell by hitting its inner wall.

c) Beam Intensity

The beam intensity is often deduced from the electric charge collected at the target. At high-precision low-current physics cyclotrons, a well-insulated charge collector (Faraday cup) can give accurate results. At production cyclotrons, however, the charge collected gives only approximate beam current because the effect of secondary electrons is not eliminated, particularly at low beam currents. The production cyclotrons are tuned to deliver relatively high currents, nominally up to 50 μA. The currents registered at the target have uncertainties of about 5% as ascertained by activation measurements. The relatively low currents needed in nuclear reaction cross-section measurements, however, are more difficult to adjust. The minimum extracted current at BC1710, for example, was about 500 nA and the uncertainty could be up to 20%. An exact measurement of the current is therefore invariably done in each experiment via the common practice of foil activation and determination of the radioactivity of a known monitor reaction product (see above).

Projectile Energy Adjustment in Sample Stacks

As mentioned earlier, most of the excitation functions of application-oriented nuclear reactions are measured today using the stacked-foil activation technique. In all those experiments, the energy of the projectile incident on the front sample is measured either via the physical method or more commonly via the activation of a monitor foil. The latter technique also gives a relatively accurate value of the incident flux of the projectile. The energies effective in the back samples are calculated using the range–energy relationship programs (see Introduction, Section "Some Special Considerations") which, however, have uncertainties. In general, the uncertainties increase with the thickness of the stack. Thus many old measurements where initial projectile energies of about 70 MeV or more were used and the stacks were rather thick to degrade the energies to 10 MeV or even lower, the calculated energies of the back samples could contain errors of several MeV. In modern methodology, therefore, not just one but a large number of monitor foils are placed interspersed in the stack. By considering the generated monitor activities, the calculated energy effective in each foil is adjusted and normalised. This procedure suggested and developed, after several IAEA-CRPs on charged-particle data evaluations, is now applied by most laboratories performing nuclear reaction cross-section measurements. The quality of the data obtained has therefore considerably improved in recent years.

The case of gas cells again needs special attention. In contrast to solid samples, in a gas target plasma is built under the impact of radiation and the gas tends to move towards the inner wall of the cell. Consequently, the gas thickness in the path

of the beam decreases and the energy calculation may contain an additional error. This effect is low at low currents but increases rapidly with the increasing beam intensity. In nuclear reaction cross-section measurement on a gas, therefore, it is strongly advised that only a low beam current is used.

Measurement of Radioactivity

Most of the radionuclides potentially useful for in vivo applications emit suitable γ-rays. In cross-section work, therefore, high-resolution HPGe detector γ-ray spectroscopy combined with efficient software for peak area analysis is now the most commonly used method for determining the radioactivity. When using samples of isotopically enriched materials, the γ-ray spectra registered are relatively clean and the peak area analysis is rather straightforward. Many experimenters, however, use only materials of natural isotopic composition. The resulting spectra are then more complex. This is especially the case when a lanthanide element is irradiated: due to the occurrence of many low-lying closely spaced nuclear levels, the γ-ray spectra encountered are complex. A very careful analysis of the spectrum is then called for.

In the case of pure β^+ emitters, that is, when no characteristic γ-ray is emitted (e.g., ^{18}F, ^{30}P), use is generally made of the 511 keV annihilation radiation, either via γ-ray spectroscopy or via $\gamma\gamma$-coincidence counting. However, since annihilation radiation is emitted by every β^+ emitter, it is absolutely necessary to carry out a full analysis of the decay curve. If two β^+ emitters of almost similar half-lives are expected, a β-spectrometric analysis is essential. In work on ^{30}P ($T_{1/2}$ = 2.5 min), for example, it was suspected that some ^{15}O ($T_{1/2}$ = 2.0 min) may be present. Measurement of $\beta^+ > 2.0$ MeV (i.e., beyond the cutoff energy of the positrons from ^{15}O) therefore yielded accurate contribution of ^{30}P.

Many radioactive products under investigation are determined quantitatively via high-resolution γ-ray spectroscopy without involving a radiochemical separation. For identification of products emitting soft radiation (e.g., ^{125}I), however, it is almost invariably necessary to isolate the radionuclide from the matrix activity. The same applies to the study of some low-lying isomeric states of a few radionuclides which are of interest in internal radiotherapy. Their decay via EC or IT is associated with the emission of Auger electrons and X-rays or low-energy γ-rays, for example, ^{117m}Sn, ^{193m}Pt, ^{195m}Pt. So a new approach to cross-section measurement has emerged. It involves a clean radiochemical separation of the product and determination of its radioactivity by high-resolution X-ray spectrometry [cf.58]. Thus, radiochemical separations are not only important in the full production process, as discussed in later chapters, but occasionally also in reaction cross-section measurements [59].

Excitation Functions and their Uncertainties

From the measured count rate of a radionuclide, extrapolated back to the end of bombardment (EOB), the absolute activity is calculated by the relation

$$A_{(\mathrm{inBq})} = \frac{\mathrm{cps} \cdot f_{\mathrm{abs}} \cdot f_{\mathrm{pile}} \cdot f_{\mathrm{coinc}}}{I_\gamma \cdot \varepsilon}$$

where cps represents counts per second, f_{abs} the corrections for self-absorption in the source and adsorption in the intervening medium between the source and the detector, f_{pile} the correction for "pile-up" of the activity, f_{coinc} the corrections for coincidence losses (random and real), I_γ the intensity of γ-ray (per decay event) and ε the efficiency of the detector for the radiation counted (considering the size and distance of the source).

From the measured radioactivity in each sample and the effective beam current the cross section of a reaction is obtained using the well-known activation equation given in Chapter 1. A plot of the cross section against the respective energy then yields the excitation function needed in the radionuclide production work.

There are three major *sources of uncertainty* in the measured excitation functions:

(i) Determination of beam current
(ii) Determination of absolute activity of the activation product
(iii) Range–energy calculation

The beam current measurement has considerably improved in recent years through the use of well-evaluated monitor reactions (see above), at least up to about 30 MeV. In general, an uncertainty of about 6% is assigned to the beam current measurement. The uncertainty in the determination of the absolute activity of the activation product arises mainly from the uncertainty in the efficiency of the counting system as well as the decay data used. In most cases, both the efficiency and the decay data are known well so that the total uncertainty due to this source generally does not exceed 3%. The uncertainty in the range–energy calculation leads to errors in the energy scale. Use of rather thick foils in the case of low energy projectiles causes considerable errors, and in the sharply increasing or decreasing section of an excitation function, it may mask the fine structure, if any. Again, as discussed above, in recent years the projectile energy adjustment in a sample stack has led to increased accuracy of the results. The reported cross sections have, in general, total uncertainties of about 8–10%; for low-yield products the total uncertainty may be up to 25%.

2.4.4 Standardisation of Charged Particle Data

It is important to evaluate and standardise the charged-particle induced reaction cross-section data to assist the user to choose proper conditions for the cyclotron production of medical radionuclides with acceptable quality. Considerable amount of experimental effort has been devoted over the last 30 years by many groups to determine reaction cross sections. All data have been compiled in the EXFOR file of the IAEA. The evaluation of those data was initiated under the

auspices of the IAEA about 20 years ago. Since no evaluation methodology existed at that time, the initial work was rather empirical. However, in later years, strong application of nuclear model codes could be built in. All the major available nuclear model codes, namely GNASH, STAPRE, ALICE-IPPE, TALYS and EMPIRE, were tried. With the exception of ALICE-IPPE, which is based purely on the exciton precompound model, all of the other codes entail a combination of compound and precompound processes.

While developing the evaluation methodology, three points clearly emerged:

(a) The need to adjust the reported formation cross sections of a radionuclide according to its latest available decay data, especially γ-ray intensities.
(b) The absolute necessity to standardise cross sections of reactions used for charged-particle flux measurement (monitor reactions). This need led to the development of a large number of monitor reactions for proton, deuteron, ^{3}He- and α-particle beams over a wide range of energies. As mentioned earlier, through the use of those monitor reactions, the accuracy of data reported in recent years from various laboratories has considerably increased.
(c) The nuclear model calculations reproduce the experimental data with varying degrees of success. They are not applicable to reactions on very light mass nuclei and are also not very successful in reproducing isomeric cross sections without special parametrization. Their main objective in the evaluation process is therefore to check the consistency in the reported data.

The finally recommended excitation function is generally based on statistical fitting of the selected experimental data. The evaluated and recommended data for the major diagnostic radionuclides are now available in ref. [53] and those for the therapeutic radionuclides in ref. [41]. They should allow a proper selection of the projectile energy range in a target to ensure high radionuclidic purity of the desired radionuclide, and the accompanying radioactive impurities can be accurately calculated. The two files are being continuously updated. Work on the evaluation of data of some novel radionuclides is in progress in several laboratories.

It should also be pointed out that the evaluated charged-particle induced nuclear reaction cross-section data need to be validated before they are finally recommended for applications. As mentioned earlier, the evaluation methodology is still developing. This is all the more so for validation methodology, which is presently only rudimentary. One option is to compare the evaluated data from enriched isotopic targets with those from the natural element, after appropriate normalisations. This method was utilized in the validation of evaluated production data for ^{124}I, ^{76}Br and ^{67}Ga. A second option is that highly enriched target material is irradiated under very well-defined conditions, and the radioactivity generated is precisely determined. A comparison of the integrally measured value with that calculated from the evaluated excitation function should then throw light on the reliability of the recommended data. Important is here, however, that

well-planned benchmark type experiments are performed, that is, a simple yield measurement in a production run is not sufficient. This type of nuclear data validation work related to charged-particle activation of materials for medical radionuclide production has hitherto not been paid much attention, but it is expected to gain more importance in the future.

2.5 Typical Examples of Charged Particle Data

2.5.1 General

The charged-particle induced reaction cross sections are dependent on several factors, for example,

- type and energy of the projectile,
- atomic mass of the target nucleus,
- type of nuclear reaction and
- level structure of the product nucleus.

Those factors are briefly discussed. In light mass target nuclei ($A \leq 25$), due to low Coulomb barrier, interactions of charged particles with nuclei are possible with high probability even at low projectile energies, leading mainly to the formation of short-lived positron emitters. In fact this characteristic of formation of positron emitters in low-energy reactions has led to the development of production of large amounts of radionuclides at small-sized cyclotrons for PET studies. The variation of the reaction cross section as a function of the projectile energy (i.e., the *excitation function*), however, often shows a resonance structure, the various peaks being attributed to preferential population of some well-separated isomeric states of the product nucleus. The results are difficult to reproduce by nuclear model calculations because of the weak contributions of statistical processes and dominance of direct interactions.

For target nuclei with mass number above 25 (especially above 40) and projectile energies up to about 30 MeV, the excitation function generally becomes smooth because of the increasing significance of the statistical processes. Most of the non-standard positron emitters, many of the SPECT radionuclides and a few therapeutic radionuclides are produced over this energy range via relatively simple reactions with high cross sections, for example, (p,xn). In case of heavy mass targets and projectiles of intermediate energy (up to about 100 MeV), more complex, relatively low-yield reactions like (p,2p), (p,αn), (p,xpyn) and others also occur and are utilized in a few cases for production of some special therapeutic radionuclides. Finally, in the heavier mass region, a few low-lying high-spin isomeric states are preferentially populated by α-particle induced reactions. With a view to elucidating the above points, some typical excitation functions are discussed below.

2.5.2 Data for Formation of Standard Positron Emitters

The four standard short-lived positron emitters (namely ^{11}C, ^{13}N, ^{15}O and ^{18}F) are commonly produced via low-energy reactions, that is, $^{14}N(p,\alpha)^{11}C$, $^{16}O(p,\alpha)^{13}N$, $^{14}N(d,n)^{15}O$, $^{18}O(p,n)^{18}F$ and $^{20}Ne(d,\alpha)^{18}F$. A summary of other reactions used earlier is to be found in Appendix I. Cross sections for the reaction $^{15}N(p,n)^{15}O$ have also been measured for its use in the production of ^{15}O utilizing a highly enriched $^{15}N_2$ target, in case the deuteron beam is not available at the cyclotron. The evaluated data for all those reactions are available in ref. [53]. A few more recently studied interesting aspects related to data for ^{18}F, ^{11}C and ^{15}O production are considered here.

The detailed excitation function for the production of **^{18}F** via the reaction $^{18}O(p,n)^{18}F$ is given in Fig. 2.9. The cross section was determined via spectroscopic measurement of the emitted neutron [44] as well as via γ-ray spectroscopic measurement of the activation product ^{18}F [60, 61]. The resolution of the resonance peaks observed in neutron spectroscopy is superior to that in the activation measurement. Nonetheless, because of better quantification of data in the activation technique, the results obtained from the ^{18}F measurement are considered to be more reliable. It is worth pointing out that in the most detailed work [61], four accelerators, namely a van de Graaff, a small cyclotron, a medium-sized cyclotron

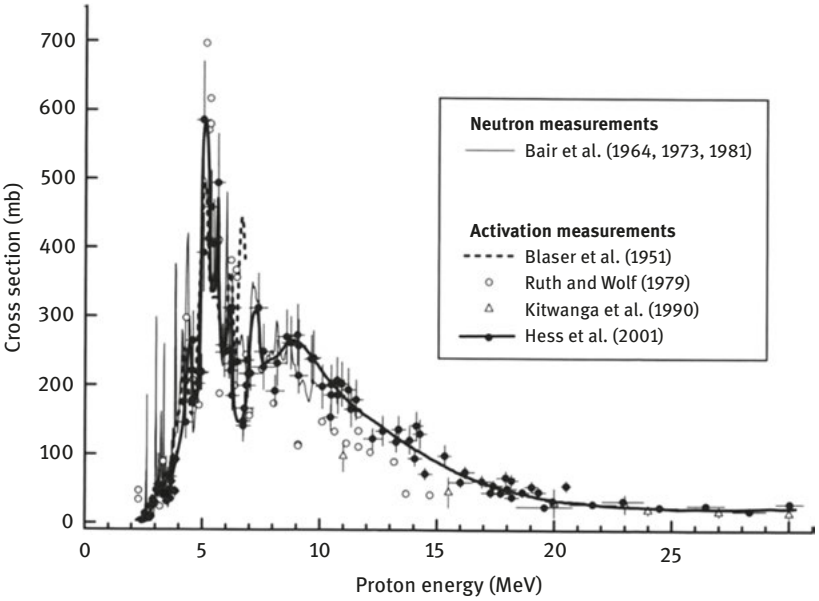

Fig. 2.9: Excitation function of the $^{18}O(p,n)^{18}F$ reaction. Results of both neutron and activation measurements are shown. The rather bold curve is an eye guide to the activation data, taken from Hess et al. [61], with courtesy of De Gruyter.

and an intermediate energy cyclotron, were used to cover the whole energy range of 2.7–30 MeV, and three types of highly enriched ^{18}O targets were utilized. They consisted of $^{18}O_2$ (gas), electrolytically prepared $Al_2{}^{18}O_3$ solid layers and thin $Si^{18}O_2$ discs. The comprehensive results shown in Fig. 2.9 now constitute the basic data for the production of the most important PET radionuclide ^{18}F using various target designs. The level of radionuclidic impurities produced is very low. Only a small amount of ^{13}N is produced via the $^{16}O(p,\alpha)$ reaction if the enrichment of ^{18}O used is not high. The integral yield of ^{18}F calculated from the excitation function is really high and so even a small cyclotron with $E_p \approx 10$ MeV can deliver large amounts of ^{18}F needed in routine PET applications (see Chapter 5).

The excitation function for the production of **^{11}C** via the commonly used reaction $^{14}N(p,\alpha)^{11}C$ also depicts several resonance peaks and was thoroughly investigated in many laboratories in the 1970s. Some newer measurements, however, revealed also the formation of the undesired radionuclides ^{14}O ($T_{½} = 70$ s) and ^{13}N ($T_{½} = 10$ min) via the reactions $^{14}N(p,n)^{14}O$ and $^{14}N(p,pn)^{13}N$, respectively [62]. The results are given in Appendix VII. Those data allow calculation of undesired amounts of the two radioactive impurities formed during the production of ^{11}C.

The case of ^{15}O is similar to that of ^{11}C. The cross sections for its formation via the $^{14}N(d,n)^{15}O$ reaction were measured and the production technology was developed already in the 1970s. Some later measurements [63] revealed the formation of the radionuclides ^{13}N and ^{11}C via the nuclear reactions $^{14}N(d,t)^{13}N$ and $^{14}N(d,\alpha n)^{11}C$, respectively. The integral yields of those two products calculated from the measured cross sections were compared with the integral yield of the major radionuclide ^{15}O, and the results are discussed in Chapter 5 dealing with the production aspects of standard radionuclides.

Thus, in short, the nuclear data for the production of standard positron emitters are well established. Yet some occasional optimisation work may still improve the quality of the product by avoiding some undesired radioactive impurities. Further-more, there are two other standard positron emitters, namely ^{68}Ga ($T_{½} = 1.15$ h) and ^{82}Rb ($T_{½} = 1.3$ min). They are produced via generator systems and are therefore treated below separately.

2.5.3 Data for Formation of Non-standard Positron Emitters

To date about 25 novel positron emitters have been developed for medical applications. The methodologies involved in the development have been reviewed (see Appendix V). Those radionuclides, like the commonly used positron emitters, are produced exclusively at cyclotrons (accelerators). The need for development of non-standard positron emitters was first realized at centres already engaged in PET studies using standard positron emitters. Since at those centres generally only a small-sized cyclotron ($E_p \leq 20$ MeV; $E_d \leq 10$ MeV) was available, the development work was oriented mainly

to low-energy nuclear reactions. The strategy of development thus became to utilize a highly enriched isotope as a target material and investigate possible production routes. In general, the low-energy (p,n) reaction on an enriched target isotope has become the common production route for most of the non-standard positron emitters. In a few cases, other low-energy reactions, such as (d,n) and (p,α), have also been employed. For a few potentially very useful positron emitters, however, intermediate energy charged-particle induced reactions are applied. The nuclear reaction cross-section data for the production of five interesting radionuclides, namely ^{64}Cu, ^{86}Y, ^{89}Zr, ^{124}I and ^{73}Se, are discussed below in some detail. They should serve as typical examples of the utilization of charged-particle beams of various energies in the production of radionuclides in the medium and heavy mass regions. The first four radionuclides have already received relatively wide application, and ^{73}Se is of great potential interest.

^{64}Cu ($T_{½}$ = 12.7 h)

Several routes have been investigated for the production of no-carrier-added ^{64}Cu. The oldest among them is the ^{64}Zn(n,p)^{64}Cu reaction in a nuclear reactor. The yield and purity of the product achieved, however, do not meet the present demands for medical applications. Proton- and deuteron-induced reactions on several target isotopes were investigated over a wide energy range of up to 80 MeV with the aim of obtaining data for the production of ^{64}Cu. Based on a critical analysis of the published nuclear reaction data, Aslam et al. [64] presented a comparison of the various production reactions of ^{64}Cu. Of all the investigated processes, the ^{64}Ni(p,n)^{64}Cu reaction, initially reported by Szelecsényi et al. [65], was found to be the best. It gives the product in high yield and with high specific activity. Its evaluated excitation function is given in Appendix VI. The threshold lies at about 3 MeV and the maximum at about 10 MeV. Thereafter, the cross section decreases due to the onset of the competing (p,2n) reaction. The optimum energy range for production is thus between 7 and 14 MeV. This energy range is within the capacity of a medical cyclotron. A comparison of the experimental data with the results of calculations using three nuclear model codes, namely EMPIRE, STAPRE and TALYS, showed good agreement. The (p,n) reaction can thus be described relatively well by nuclear model calculations (see Fig. 1 in Appendix VI). The result shows that, if many data points are available, a theory-based selection of the data is possible. A polynomial fit or any other fit to the selected data then gives the recommended curve.

^{86}Y ($T_{½}$ = 14.7 h)

Several nuclear reactions have been investigated for the formation of this radionuclide but the studies have not been exhaustive. Two critical evaluations of data for some of the important reactions were performed [66, 67]. The recommended method for the production of ^{86}Y is the originally proposed ^{86}Sr(p,n)^{86}Y reaction [68] on

a highly enriched target. Its excitation function is given in Fig. 2.10. The experimental cross-section data are compared with the results of nuclear model calculations using three standard codes, namely ALICE-IPPE, TALYS and EMPIRE. All the codes describe the shape of the excitation function rather well but the magnitudes are different. It is evident that the scatter in the experimental data is large and more precise measurements are called for. On the other hand, despite this deficiency, the production methodology is established (see Chapter 6).

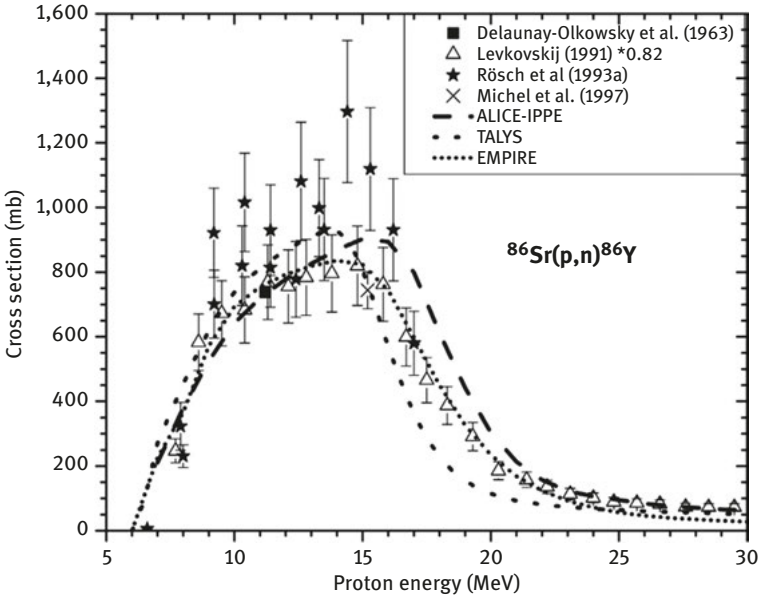

Fig. 2.10: Normalised experimental data for the ^{86}Sr(p,n)^{86}Y reaction along with the results of three nuclear model calculations, viz. ALICE-IPPE, TALYS and EMPIRE, shown as a function of proton energy, taken from Zaneb et al. [66], with permission from Elsevier.

^{89}Zr ($T_{½}$ = 78.4 h)

The main nuclear reaction used for the production of ^{89}Zr is the ^{89}Y(p,n)^{89}Zr process. It has been investigated by several groups and a summary of the cross-section data is given in ref. [69]. Except for a few data points, most of the results appear to agree well. A critical evaluation may help in solving the small discrepancies. The method is very advantageous: it can be used at a small-sized cyclotron and the target material ^{89}Y is monoisotopic.

^{124}I ($T_{½}$ = 4.18 d)

For production of ^{124}I, initially the reaction ^{124}Te(d,2n)^{124}I was used. Later on, cross sections of the reactions ^{124}Te(p,n)^{124}I, ^{125}Te(p,2n)^{124}I, ^{126}Te(p,3n)^{124}I as well as of ^{3}He- and α-particle induced reactions on antimony (naturally and isotopically enriched isotopes) were measured over energy ranges of up to 100 MeV. A critical analysis of all the reactions was performed and it was concluded that the ^{124}Te(p,n)^{124}I reaction, originally suggested by Scholten et al. [70] is the most suitable for the production of ^{124}I. The cross-section data for protons on 99.8% enriched ^{124}Te [70] are shown as excitation curves in Fig. 2.11. The suitable energy range for the production of ^{124}I is E_p = 12 → 8 MeV. The product obtained is of the highest radionuclidic purity. If the production of the radionuclide ^{123}I is desired, the suitable energy range would be E_p = 25 → 18 MeV. These data thus clearly depict the practical application of the excitation functions: by using a sharp energy window it is possible to obtain a desired radionuclide in a pure form.

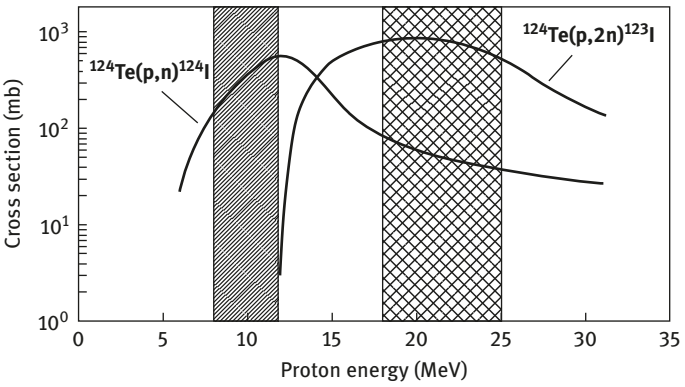

Fig. 2.11: Excitation functions of ^{124}Te(p,n)^{124}I and ^{124}Te(p,2n)^{123}I reactions. The curves are based on data reported by Scholten et al. [70]. The suitable energy range for the production of ^{123}I is E_p = 25.0 → 18.0 MeV and that for ^{124}I it is E_p = 12 → 8 MeV.

^{73}Se ($T_{½}$ = 7.1 h)

In contrast to the production of the above mentioned four non-standard positron emitters via the low-energy (p,n) reaction, for the formation of ^{73}Se several nuclear processes have been investigated, for example, ^{75}As(p,3n)^{73}Se, ^{75}As(d,4n)^{73}Se, ^{72}Ge(^{3}He,2n)^{73}Se and ^{70}Ge(α,n)^{73}Se. They all need intermediate energy projectiles. Recently, a critical analysis of the cross-section data of all those reactions was performed [32] and the relevant excitation functions are reproduced in Fig. 2.12. The (α,n) reaction has the highest cross section. The calculated thick target yields, however, showed that due to the very short range of α-particles, the (α,n)

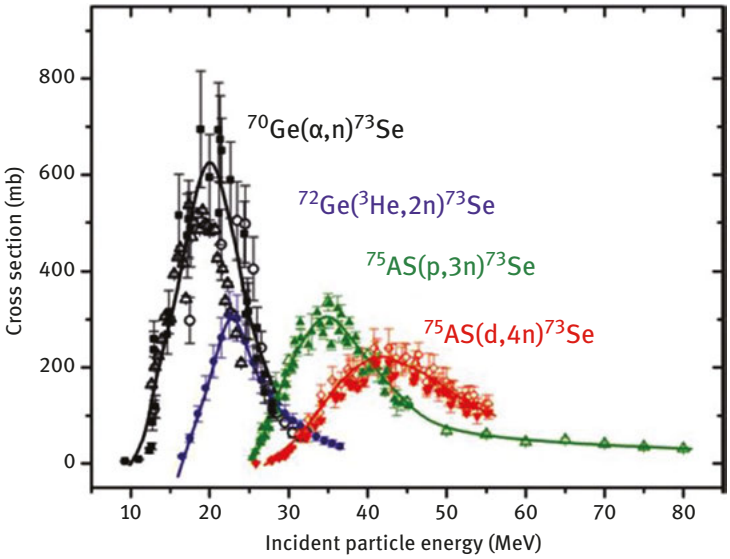

Fig. 2.12: Excitation functions of a few nuclear reactions in the intermediate energy range used for the production of ^{73}Se, taken from Qaim et al. [32], with courtesy of De Gruyter.

reaction is not very advantageous [32]. Considering the levels of the associated longer lived impurities ^{75}Se ($T_{½}$ = 120.0 d) and ^{72}Se ($T_{½}$ = 8.5 d), it was concluded that the ^{75}As(p,3n)^{73}Se reaction over the energy range of E_p = 40 → 30 MeV, originally suggested by Mushtaq et al. [71] is most suited, the levels of the ^{75}Se and ^{72}Se impurities being 0.05% and 0.11%, respectively, of the amount of ^{73}Se. This method has also the advantage that the target material arsenic is monoisotopic.

Other Non-standard Positron Emitters

Besides the above-discussed five non-standard positron emitters, several others are also finding increasing attention. Using a low-energy cyclotron, investigations are underway on ^{43}Sc ($T_{½}$ = 3.9 h), ^{44}Sc ($T_{½}$ = 3.9 h), ^{45}Ti ($T_{½}$ = 3.1 h), ^{52}Mn ($T_{½}$ = 5.6 d), ^{55}Co ($T_{½}$ = 17.5 h), ^{61}Cu ($T_{½}$ = 3.3 h), ^{66}Ga ($T_{½}$ = 9.5 h), ^{72}As ($T_{½}$ = 26.0 h), ^{76}Br ($T_{½}$ = 16.2 h), ^{94m}Tc ($T_{½}$ = 52 min), ^{120}I ($T_{½}$ = 1.3 h) and so on. Their nuclear data are known to some extent and the status has been reviewed [36]; the data near the thresholds are somewhat uncertain. For development of a few other novel positron emitters, use of intermediate energy reactions is necessary. In particular, the production of ^{52}Fe ($T_{½}$ = 8.3 h), ^{57}Ni ($T_{½}$ = 36.0 h), ^{77}Kr ($T_{½}$ = 1.2 h), ^{83}Sr ($T_{½}$ = 32.4 h) and ^{152}Tb ($T_{½}$ = 17.5 h) by the nuclear reactions ^{55}Mn(p,4n)^{52}Fe, ^{59}Co(p,3n)^{57}Ni, ^{79}Br(p,3n)^{77}Kr, ^{85}Rb(p,3n)^{83}Sr and ^{155}Gd(p,4n)^{152}Tb, respectively, demands cyclotrons accelerating

proton energies up to about 100 MeV. The cross-section data of some of those reactions are known, but in many cases more extensive measurement and evaluation programs are needed.

2.5.4 Data for Formation of Standard Photon Emitters

A large number of γ-ray emitting radionuclides have found application in diagnostic nuclear medicine using either γ-cameras or, in recent years, mainly SPECT. The production cross sections of the five major ones listed in Table 1.1 are discussed here.

The most commonly used SPECT radionuclide **^{99m}Tc** ($T_{1/2}$ = 6.0 h) is commercially available on a routine basis via the ^{99}Mo/^{99m}Tc generator, the ^{99}Mo being produced in a nuclear reactor using one of the two processes, namely ^{98}Mo(n,γ)^{99}Mo and ^{235}U(n,f)^{99}Mo. The cross-section data of those processes have been discussed earlier (see Sections 2.3.1 and 2.3.2). In recent years, the apprehension of shortage in the supply of this radionuclide, due to possible shutdown of nuclear research reactors, has led to considerable efforts to develop alternative production methods (for a discussion cf. [72]). Among the charged-particle induced reactions, the ^{100}Mo(p,2n)-^{99m}Tc process appears to be very promising. A large number of cross-section measurements have been done and a critical evaluation of all data has been performed [73]. The evaluated curve for this reaction is shown in Fig. 2.13 together with the calculated results for the formation of two other long-lived Tc isotopes. The energy range E_p = 22 → 10 MeV appears to be optimum for the cyclotron production of ^{99m}Tc. However, the level of ^{99g}Tc ($T_{1/2}$ = 2.1 × 10^5 a) will be considerably higher than that via the ^{99}Mo/^{99m}Tc generator system. Furthermore, some ^{98}Tc ($T_{1/2}$ = 4.2 × 10^6 a) may also be formed.

The four other major SPECT radionuclides, namely ^{67}Ga ($T_{1/2}$ = 3.26 d), ^{111}In ($T_{1/2}$ = 2.81 d), ^{123}I ($T_{1/2}$ = 13.2 h) and ^{201}Tl ($T_{1/2}$ = 3.06 d), are routinely produced at a medium-sized cyclotron. For each radionuclide, many reactions were investigated (see Appendix I). Today, the metallic radionuclides **^{67}Ga** and **^{111}In** are routinely produced via the (p,2n) reactions on isotopically enriched targets ^{68}Zn and ^{112}Cd, respectively. The excitation functions of both the reactions are well documented by experimental studies. They have also been well evaluated using both nuclear model calculations and fitting methods [53]. The same applies to **^{201}Tl**. In this case, however, the nuclear route of interest is the process $^{203}\mathrm{Tl}(\mathrm{p},3\mathrm{n})^{201}\mathrm{Pb} \xrightarrow[9.4\mathrm{h}]{EC} {}^{201}\mathrm{Tl}$, that is, the desired product is obtained via the decay of the reaction product ^{201}Pb. The optimum conditions for its production were described rather early (see Appendix I); in particular, the level of the ^{200}Tl impurity in ^{201}Tl as a function of incident proton energy was established. Some newer cross-section measurements have strengthened the database and recommended cross sections are now available [39, 53].

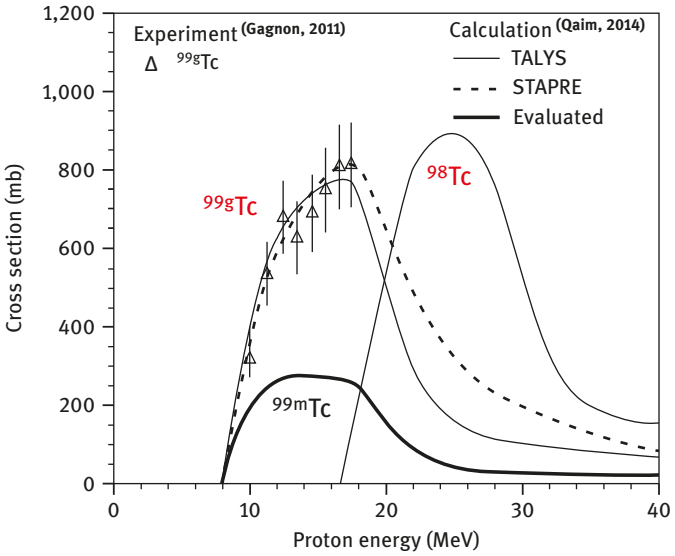

Fig. 2.13: Excitation functions of proton induced nuclear reactions on ^{100}Mo. The curve for the reaction ^{100}Mo(p,2n)^{99m}Tc is based on an evaluation of all reported experimental data. For the reactions ^{100}Mo(p,2n)^{99g}Tc and ^{100}Mo(p,3n)^{98}Tc, the available experimental data [74] and the results of nuclear model calculations are shown; taken from Qaim et al. [73], with permission from Elsevier.

For the production of **^{123}I**, about 25 nuclear processes were investigated (for early review, see Appendix II). Among them only four are of significance. At low energy cyclotrons, the ^{123}Te(p,n) reaction over E_p = 14.5 → 10 MeV is applied and at medium-energy cyclotrons, the ^{124}Te(p,2n) process over E_p = 25 → 18 MeV (cf. Fig. 2.11). In either case, highly enriched target material is used. The disadvantages of the (p,n) process are the low ^{123}I yield and the relatively high ^{124}I impurity, if ^{123}Te of low enrichment is used. The ^{124}I impurity level is still higher in the case of the (p,2n) route. The third route of ^{123}I-production consists of the $^{127}\mathrm{I}(\mathrm{p},5\mathrm{n})^{123}\mathrm{Xe} \xrightarrow[2.1\ \mathrm{h}]{EC} {}^{123}\mathrm{I}$ process. The optimum energy range for this route is E_p = 65 → 45 MeV. This is a relatively high yield process and the only impurity observed is ^{125}I (~0.25%). The cross-section data have been evaluated, and recommended values are available [53]. There are still some discrepancies in the data. The fourth route of ^{123}I-production consists of the ^{124}Xe(p,x) process. It involves the use of highly enriched ^{124}Xe as target, but requires only a medium-sized cyclotron. In contrast to the above mentioned three routes, this process leads to ^{123}I of the highest purity. The natural abundance of ^{124}Xe is only 0.1%; consequently, the highly enriched ^{124}Xe is very expensive. The production method has been well developed, though some discrepancies in the cross-section data still exist. The formation of ^{123}I occurs through three

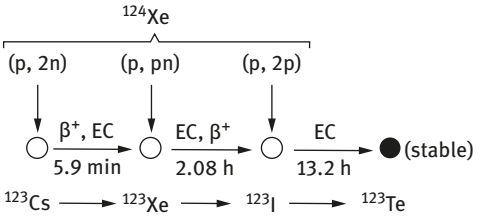

Fig. 2.14: Nuclear routes contributing to the formation of ^{123}I in the irradiation of highly enriched ^{124}Xe gas with 30 MeV protons.

contributing processes shown in Fig. 2.14. The major contribution is furnished by the ^{124}Xe(p,2n)^{123}Cs reaction, whereby the reaction product ^{123}Cs decays rapidly to ^{123}Xe. The second contributing reaction is the ^{124}Xe(p,pn)^{123}Xe process. Thus, ^{123}Xe is formed directly as well as via the decay of the precursor ^{123}Cs.

The decay of ^{123}Xe then leads to the product ^{123}I, which is also partly formed directly through the ^{124}Xe(p,2p)^{123}I reaction. The contribution of the latter reaction to the formation of ^{123}I was, however, found to be <5%; the contributions of the (p,2n) and (p,pn) reactions amounting to approximately 75% and 20–25%, respectively. Only three measurements have been reported [75–77]. The data for the (p,2n) reaction are well characterised, partly using the radiochemical technique. In the case of the (p,pn) reaction, the three reported cross-section values differ widely. An updated evaluation [39] does not solve the problem. The major problem is that the directly formed ^{123}Xe is much smaller in quantity than that formed via the decay of the ^{123}Cs precursor. By the time ^{123}Xe is measured, it contains appreciable contribution from the decaying precursor. Thus, the independent formation cross section has appreciable uncertainty. A sophisticated radiochemical investigation involving a fast removal of the short-lived ^{123}Cs followed by measurement of the ^{123}Xe radioactivity may remove the discrepancy. On the other hand, despite this discrepancy, the optimum energy range for the production of ^{123}I via this route was deduced as $E_p = 29 \rightarrow 23$ MeV [76].

New Development

Regarding the γ-ray emitting radionuclides, a new emerging aspect is worth mentioning. It relates to the use of SPECT for imaging the dose distribution in Auger therapy with ^{67}Ga and ^{111}In, and in β^- therapy with radionuclides like ^{177}Lu ($T_{1/2}$ = 6.7 d) and ^{186}Re ($T_{1/2}$ = 3.78 d). Those β^--emitting therapeutic radionuclides emit γ-rays of energies 208.4 and 137.2 keV, respectively, which allow convenient use of SPECT for semi-quantitative determination of the activity distribution in an organ. The same may apply also to several other developing therapeutic radionuclides (see Chapter 6). However, since the emphasis in those cases is on therapy and not on diagnosis via SPECT, the production data of those radionuclides are considered under the topic of therapeutic radionuclides.

2.5.5 Data for Formation of Standard Radionuclides for Internal Radiotherapy

Most of the radionuclides used in internal radiotherapy are produced using neutron induced reactions. However, in recent years, charged-particle induced reactions are also finding increasing applications in the production of some therapeutic radionuclides, particularly those emitting low-range but highly ionizing radiation. Among them are the radionuclides ^{67}Cu ($T_{½}$ = 2.58 d), ^{186}Re ($T_{½}$ = 3.78 d), ^{211}At ($T_{½}$ = 7.2 h), ^{225}Ac ($T_{½}$ = 10.0 d), ^{117m}Sn ($T_{½}$ = 13.6 d), ^{77}Br ($T_{½}$ = 2.37 d), ^{193m}Pt ($T_{½}$ = 4.33 d), ^{195m}Pt ($T_{½}$ = 4.02 d) and ^{103}Pd ($T_{½}$ = 17.0 d). The radionuclides ^{67}Cu and ^{186}Re are low-energy β^- emitters, ^{211}At and ^{225}Ac are α-emitters, ^{77}Br, ^{193m}Pt and ^{195m}Pt are Auger electron emitters and ^{103}Pd is an X-ray emitter.

The radionuclide **^{77}Br** was originally used in SPECT studies but recently interest has been growing in its application in Auger therapy. This radionuclide as well as **^{211}At** have been produced for several decades via the ^{75}As(α,2n)^{77}Br and ^{209}Bi(α,2n)^{211}At reactions, respectively (see Appendix II and ref. [53]), and the excitation functions are well documented, both experimentally and through nuclear model calculations. The radionuclide ^{77}Br was also produced in low yield but high purity through the route $^{79}\mathrm{Br}(\mathrm{d},4\mathrm{n})^{77}\mathrm{Kr}\xrightarrow[1.2\ \mathrm{h}]{EC,\ \beta^+}{}^{77}\mathrm{Br}$ [46]. An exhaustive analysis of all reactions considered for the production of ^{77}Br is given in ref. [78]. Considerable efforts have been or are being devoted to production of the remaining seven radionuclides through charged-particle induced reactions. The relevant production data are discussed below individually.

^{67}Cu ($T_{½}$ = 2.58 d)

Many of the suggested methods for the production of this β^--emitting radionuclide have been reviewed [79]. The cross-section data for its production via the ^{67}Zn(n,p)^{67}Cu reaction have been discussed in detail [36, 72]. Four routes induced by charged particles, namely ^{70}Zn(p,α)^{67}Cu, ^{70}Zn(d,αn)^{67}Cu, ^{68}Zn(p,2p)^{67}Cu and ^{64}Ni(α,p)^{67}Cu, were investigated: the first two at a low-energy cyclotron and the latter two at an intermediate energy cyclotron or accelerator. In each case a highly enriched target is necessary. The cross-section data for the ^{70}Zn(p,α)^{67}Cu and ^{68}Zn(p,2p)^{67}Cu reactions have been evaluated [41] and the database of the other reactions is weak. Furthermore, there are some discrepancies in the data. The ^{68}Zn(p,2p)^{67}Cu reaction over the energy range E_p = 70 → 30 MeV appears to be more suitable (see Appendix VI). Presently, a few neutron and photon induced reactions are also being developed for production of this important radionuclide. The production possibilities using those routes are discussed later in Chapter 6.

^{186}Re ($T_{1/2}$ = 3.78 d)

This radionuclide decays 92.5% by β^- emission and 7.5% by EC. The endpoint energy of β^- particles is 1070 keV. A γ-ray of energy 137 keV (I_γ = 9.5%) is also emitted. This radionuclide was originally produced via the ^{185}Re(n,γ)^{186}Re reaction but the specific activity was low. It is being superseded by the ^{186}W(p,n)^{186}Re process. Many groups have reported reaction cross sections. Calculations done using three nuclear model codes, namely STAPRE, EMPIRE and TALYS, reproduce most of the data well (see Fig. 4 in Appendix VII). Based on a critical discussion [80], it was concluded that high-purity ^{186}Re can be obtained only by using a highly enriched ^{186}W target and the maximum proton energy of 18 MeV. This radionuclide can also be produced via the ^{186}W(d,2n)^{186}Re reaction but the cross-section database is weaker [80].

^{225}Ac ($T_{1/2}$ = 10.0 d)

There is great interest in this α-particle emitting radionuclide; it is useful in itself as well as for providing ^{213}Bi ($T_{1/2}$ = 46 min; E_α = 5900 keV) through a generator system. Regarding its production using charged particles, two processes are presently under investigation. The first one is the ^{226}Ra(p,2n)^{225}Ac reaction on the radioactive target material ^{226}Ra. Only one cross-section measurement exists [81] and the database is weak. The second method involves the irradiation of ^{232}Th with intermediate energy protons [82–86] and the cross sections for the formation of ^{225}Ac are shown in Fig. 2.15. The optimum energy range for the production of ^{225}Ac is deduced to be E_p = 140 → 60 MeV.

^{117m}Sn ($T_{1/2}$ = 13.6 d)

The high-spin isomeric state (I = 11/2$^-$) of ^{117m}Sn, lying at 314.6 keV above the ground state, decays by two transitions in cascade. The first of these (156 keV) is highly internally converted but the second one leads to a 159 keV γ-ray (I_γ = 86.4%). This radionuclide was therefore initially of interest for SPECT studies. In later years, the interest changed because the emitted conversion electrons of energies 151.6 keV (27.4%), 129.4 keV (11.9%) and 127 keV (66.3%) are well suited for internal therapeutic applications.

For some palliative applications, the carrier-added products obtained via the ^{116}Sn(n,γ)^{117m}Sn and ^{117}Sn(n,n´γ)^{117m}Sn processes have been commonly used. The effective cross section of the first reaction (considering σ_{th} and I_0) is low (19.5 ± 2.0 mb), but the neutron fission spectrum-averaged cross section of the latter reaction is much higher (222 ± 16 mb) [87]. The ^{117}Sn(n,n´γ)^{117m}Sn route using a highly enriched target thus leads to higher specific activity. Nonetheless, in order to obtain no-carrier-added ^{117m}Sn, charged-particle induced reactions were investigated. The status of data was reviewed [36, 72]. Among them the ^{116}Cd(α,3n)^{117m}Sn reaction appears to be the most suitable. The cross section is high, apparently due

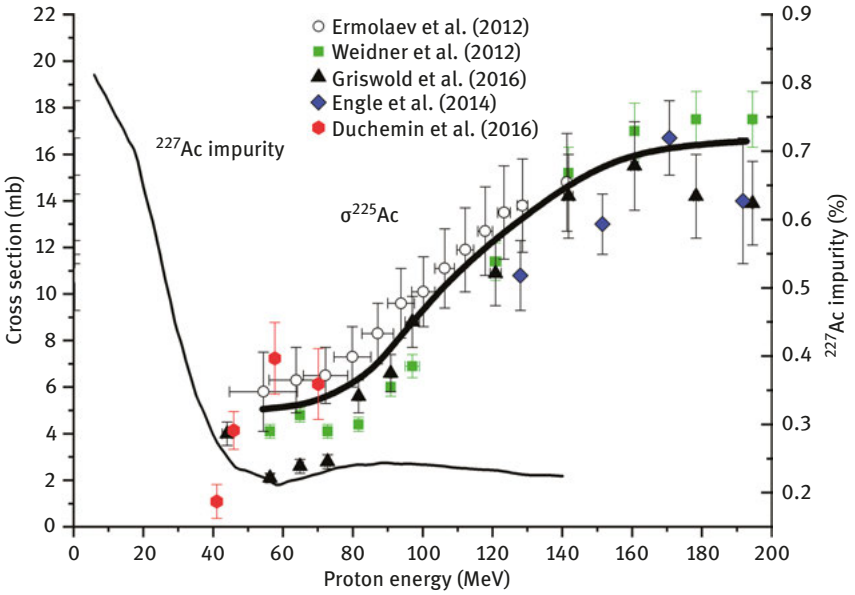

Fig. 2.15: Cross-section data [82–86] (left scale) for the formation of ^{225}Ac in irradiation of ^{232}Th with intermediate energy protons shown as a function of projectile energy. The thick solid line is an eye guide. The level of the ^{227}Ac impurity (thin solid line, right scale) is also given [82].

to the preferential population of the high-spin isomer in the α-particle induced reaction [32]. The evaluated excitation function [88] based on consistent experimental data [89–92] is reproduced in Fig. 2.16. The optimum energy range for the production of ^{117m}Sn is deduced to be $E_\alpha = 45 \rightarrow 25$ MeV. A discussion of other production aspects is given in Chapter 6.

^{193m}Pt ($T_{½}$ = 4.33 d) and ^{195m}Pt ($T_{½}$ = 4.02 d)

These two radionuclides are pure X-ray and Auger electron emitters, each decay leading to more than 30 secondary electrons, with their energies distributed between 10 and 130 keV. They have thus great potential in Auger electron therapy. The reactor production routes, namely the ^{192}Pt(n,γ)^{193m}Pt and ^{195}Pt(n,n´γ)^{195m}Pt reactions, lead to low specific activity, even while using enriched targets. This is due to relatively low cross sections [87] for the formation of these two high-spin isomers in low-energy neutron induced reactions. The production of ^{195m}Pt via the ^{192}Os(α,n) reaction was investigated but the cross section is too low. However, the production of ^{193m}Pt via the ^{192}Os(α,3n)^{193m}Pt reaction on a highly enriched target appears to be very promising. The results of a radiochemical measurement employing X-ray spectrometry [58] showed that the cross section of the reaction is

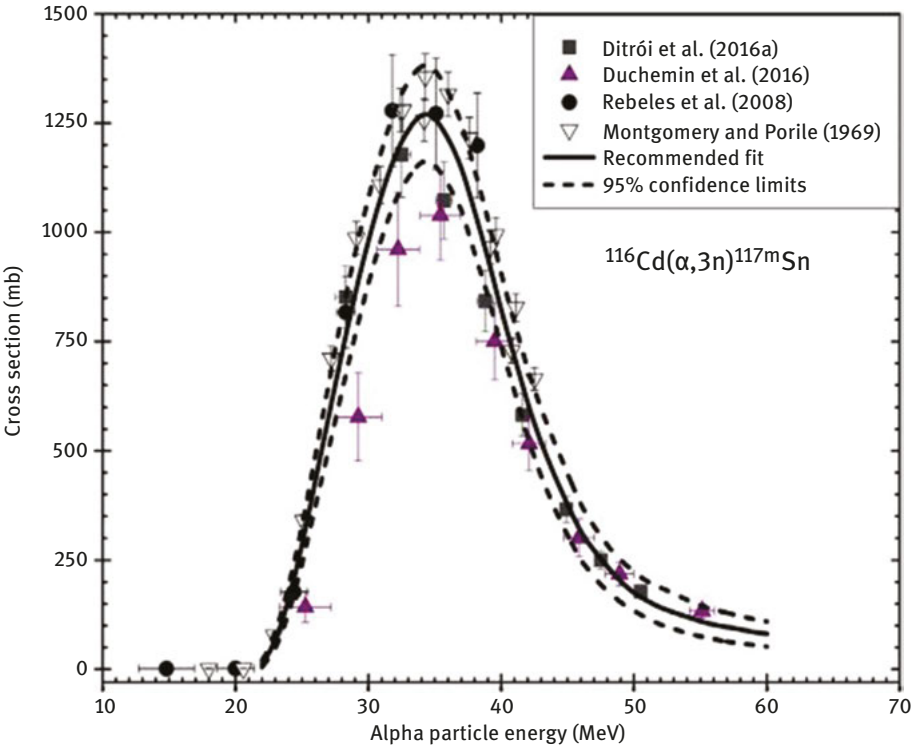

Fig. 2.16: Evaluated excitation function of the reaction ^{116}Cd(α,3n)^{117m}Sn based on consistent experimental data [89–92], taken from Aslam et al. [88], with permission from Elsevier.

fairly high, presumably due to the favourable population of the high-spin (13/2$^+$) ^{193m}Pt (see Fig. 3 in Appendix VI). The optimum energy range for its production is deduced to be E_α = 40 → 30 MeV. The nuclear database, however, needs further strengthening.

^{103}Pd ($T_{½}$ = 17.0 d)

This radionuclide is a pure X-ray emitter with a few Auger electrons. It was originally produced using the ^{102}Pd(n,γ)^{103}Pd reaction. The cross-section data are known [38]. However, due to the low percentage of ^{102}Pd (1.02%) in natural palladium, the specific activity of the product achieved was very low. The method has therefore been superseded by the ^{103}Rh(p,n)^{103}Pd reaction at a cyclotron. The cross-section data were obtained using neutron detection as well as measurement of the activation product. In the latter case, both γ-ray and X-ray spectrometry were applied. The results of an evaluation [93] are shown in Fig. 2.17. More

reliance was placed on data obtained by X-ray spectrometry because the intensity of the 357 keV γ-ray used (I_γ = 0.0221%) is very low. The optimum energy range for the production of ^{103}Pd was deduced as E_p = 16 → 7 MeV. This method is extensively used in large-scale production of ^{103}Pd. The production was also investigated using the ^{103}Rh(d,2n)^{103}Pd reaction and the ^{nat}Ag(p,x)^{103}Pd process. The database for the latter reaction, however, is as yet not very strong.

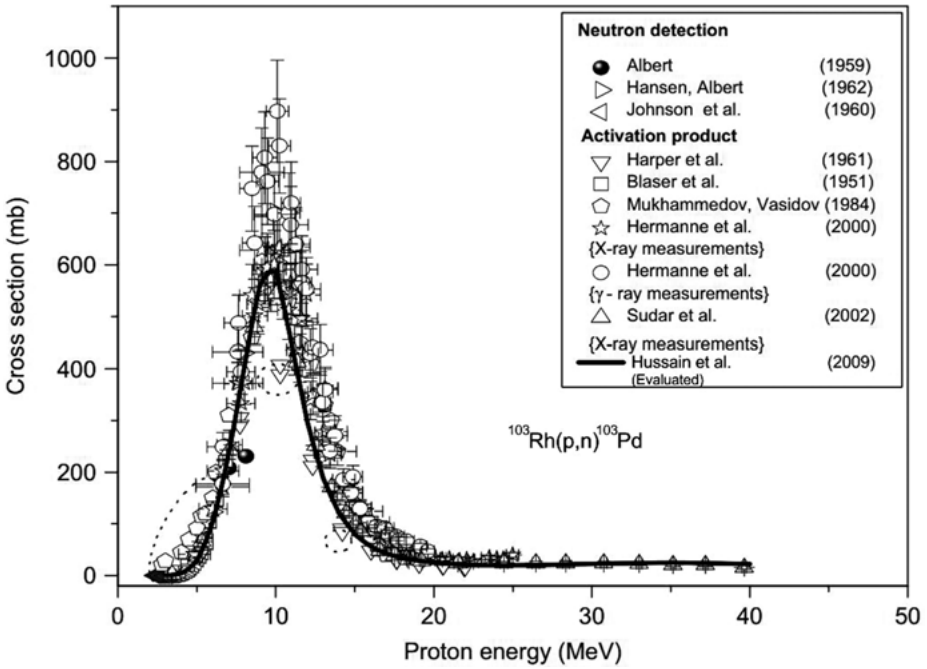

Fig. 2.17: Experimental data and the evaluated excitation function of the reaction ^{103}Rh(p,n)^{103}Pd, taken from Hussain et al. [93], with permission from Elsevier.

Other Therapeutic Radionuclides

In addition to the above-mentioned nine typical therapeutic radionuclides (viz. ^{77}Br, ^{211}At, ^{67}Cu, ^{186}Re, ^{225}Ac, ^{117m}Sn, ^{193m}Pt, ^{195m}Pt and ^{103}Pd) being produced via charged-particle induced reactions, several others are also considered to be of great potential use, and the relevant development work is going on. For example, the production of the low-energy β^- emitter ^{47}Sc ($T_{1/2}$ = 3.35 d) via the ^{48}Ti(p,2p)^{47}Sc reaction is attracting attention. Regarding targeted α-particle therapy, ^{226}Th ($T_{1/2}$ = 31 min) is receiving some attention. It can be obtained through a generator column loaded with ^{230}U ($T_{1/2}$ = 20.8 d), which is also an α-emitter and is produced through the $^{232}\mathrm{Th}(\mathrm{p},3\mathrm{n})^{230}\mathrm{Pa} \xrightarrow{\beta} {}^{230}\mathrm{U}$ process. A rather exotic α-particle emitter, namely ^{149}Tb

($T_{1/2}$ = 4.1 h), has also been used in a special investigation. It is difficult to produce; to date only a heavy-ion induced reaction or the spallation process has been utilized. Similarly the radionuclide ^{140}Nd ($T_{1/2}$ = 3.37 d) is considered to be interesting for Auger therapy. It is produced via the ^{141}Pr(p,2n)^{140}Nd reaction. Thus, the use of accelerators in development of radionuclides for internal radiotherapy is enhancing. The cross-section database, however, in most of the cases is rather weak and further detailed measurements are needed.

2.5.6 Data for Formation of Standard Generator Parent Radionuclides

As mentioned earlier, two important reactor-produced generator systems, namely ^{99}Mo/^{99m}Tc and ^{90}Sr/^{90}Y, are extensively used in diagnosis and internal radiotherapy, respectively. Their nuclear databases are well established. As regards cyclotron-produced systems, a comprehensive review dealing with all potentially useful generator systems and possible production reactions of the parent nuclides was published already in 1987 (see Appendix III). In the meantime, several of those systems have received more attention [94]. Today, two generator-produced positron emitters, namely ^{68}Ga ($T_{1/2}$ = 1.15 h) and ^{82}Rb ($T_{1/2}$ = 1.3 min), are routinely used in diagnostic studies and are now considered as "standard PET radionuclides." They are available via the generator systems ^{68}Ge(271.0 d)/^{68}Ga and ^{82}Sr (25.3 d)/^{82}Rb, respectively. Originally, the two parent radionuclides (^{68}Ge and ^{82}Sr) were produced via the spallation process. In recent years, however, production methodologies have been modified and the two radionuclides are now generated using an intermediate energy accelerator/cyclotron.

For production of ^{68}Ge, the method used now is the ^{nat}Ga(p,x)^{68}Ge process. Its excitation function is known (cf. Fig. 8 in Appendix V). The database is not very strong and further measurements are needed. Nonetheless, it is obvious that the first peak at about 21 MeV is due to the ^{69}Ga(p,2n)^{68}Ge reaction, and the second bump beyond 35 MeV originates from the contribution of the ^{71}Ga(p,4n)^{68}Ga process. Thus using an enriched ^{69}Ga target, the energy range suitable for the production of ^{68}Ge would be E_p = 28 → 12 MeV, whereas in the case of a ^{nat}Ga target, a broader energy range E_p = 50 → 12 MeV could be used. In the latter case, however, considerable amount of the longer lived impurity ^{71}Ge ($T_{1/2}$ = 11.4 d) would also be formed.

For production of ^{82}Sr, either the ^{85}Rb(p,4n)^{82}Sr reaction or the ^{nat}Rb(p,xn)^{82}Sr process is utilized. The excitation functions of the ^{85}Rb(p,4n)^{82}Sr and other competing reactions on enriched ^{85}Rb were measured up to 100 MeV (cf. Fig. 7 in Appendix V). The optimum energy range for the production of ^{82}Sr was deduced to be E_p = 70 → 50 MeV. A small amount of the radionuclide ^{85}Sr ($T_{1/2}$ = 64.9 d) is formed as impurity and its check is necessary. The cross-section data reported for a ^{nat}Rb target [95] are shown in Fig. 2.18. Since in a real production run generally ^{nat}RbCl is used as the

target material, it is very critical to control the energy range within the target so that the level of the ^{85}Sr activity is not too high. It is recommended that the proton energy within the target should always remain above 50 MeV.

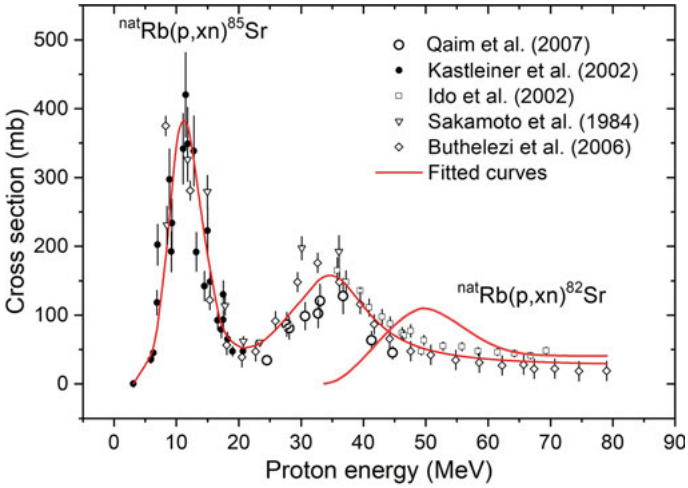

Fig. 2.18: Excitation functions of the reactions ^{nat}Rb(p,xn)^{85}Sr and ^{nat}Rb(p,xn)^{82}Sr processes. For the latter process only the fitted curve is shown. Diagram adapted from Qaim et al. [95], with permission from Elsevier.

Besides the above-mentioned two established generator systems for the supply of the positron emitters ^{68}Ga and ^{82}Sr, four other cyclotron-produced generators have also found some application. They are ^{62}Zn (9.2 h)/^{62}Cu (10.0 min), ^{122}Xe (20.1 h)/^{122}I (3.6 min), ^{81}Rb (4.6 h)/^{81m}Kr (13.1 s) and ^{178}W (22.0 d)/^{178}Ta (9.3 min), the first two being applied in PET studies and the latter in γ-scintigraphy. The first and the third are even clinically established. Their parents are produced via the ^{63}Cu(p,2n)^{62}Zn and ^{82}Kr(p,2n)^{81}Rb reactions, and the database is fairly good [53], yet because of their short half-lives, the use of the corresponding generator system has been rather limited. Due to difficulties in producing ^{122}Xe via the ^{127}I(p,6n) reaction and ^{178}W via the ^{181}Ta(p,4n) reaction, the use of the ^{122}Xe/^{122}I generator system has been still more limited. The database of the reaction for the production of ^{122}Xe is fairly good (see Appendix III) but of the reaction for the production of ^{178}W is weak [96, 97].

Presently, a few potentially important generator systems are also in development, especially ^{44}Ti (60.4 a)/^{44}Sc (3.9 h) and ^{72}Se (8.5 d)/^{72}As (26.0 h). The promising nuclear reactions for the production of the parent nuclides ^{44}Ti and ^{72}Se are ^{45}Sc(p,2n)^{44}Ti and ^{75}As(p,4n)^{72}Se, respectively. The excitation function for the

formation of ^{44}Ti has been measured (cf. Fig. 8 in Appendix V), but for ^{72}Se, data have been reported only up to about 45 MeV [71] Thus, in the case of ^{44}Ti the database is weak, and in the case of ^{72}Se it is incomplete and needs to be extended up to about 60 MeV. Nonetheless, using a high-intensity intermediate energy cyclotron it should be possible to produce both the parent radionuclides for research applications.

2.6 Some Other Issues Related to Charged-Particle Induced Reactions

Three other issues are of importance while considering cross sections of charged-particle induced reactions. They are related to use of multiparticle cyclotrons, use of intermediate energy proton accelerators and formation of isomeric states in final products. Those issues were recently discussed [36]. A brief description is given below.

2.6.1 Use of Multiparticle Cyclotrons

As described earlier, clinical-scale production of most of the β^+ emitters, especially the non-standard β^+ emitters, is carried out at medical cyclotrons using the (p,n) reaction on the respective highly enriched target material. On the other hand, the production of the SPECT radionuclides is carried out at a medium-sized cyclotron using 30 MeV protons. Furthermore, for the production of a few radionuclides, the α-particle beam is absolutely needed, for example, ^{30}P, ^{38}K, ^{77}Br and ^{211}At [32]. A few Auger and conversion electron emitters, for example, ^{193m}Pt and ^{117m}Sn, are also preferentially formed in α-particle induced reactions. Similarly, the use of a deuteron beam appears to be attractive for the production of a few radionuclides. For example, the production of ^{103}Pd and ^{186}Re via the (d,2n) reaction in comparison to the presently used (p,n) reaction is being favoured because, for a given energy, the yield via the (d,2n) reaction is higher (see Appendix IV and ref. [93]). It should, however, be pointed out that the available deuteron energies and intensities at small medical cyclotrons are not sufficient for production purposes. Some efforts are, nonetheless, underway to develop high intensity medium-sized deuteron accelerators. Thus, it is expected that medium-sized multiparticle cyclotrons will continue to play an important role.

2.6.2 Use of Intermediate Energy Proton Accelerators

Nuclear reactions induced by protons of energies up to about 150 MeV are already used today to produce a few special radionuclides, for example, ^{52}Fe, ^{67}Cu and ^{225}Ac. Several other radionuclides could also be produced. The nuclear data needs in the intermediate energy range are expected to increase continuously.

In a few limited laboratories, the spallation process with 500–1000 MeV protons was also studied to produce radionuclides, for example, ^{68}Ge, ^{77}Br and ^{82}Sr. However, the conventional chemical separation methods were not adequate and the product contained impurities. Therefore, today no radionuclide is produced via this method in sufficient quantity and acceptable quality for broader use. In recent years, however, the spallation process combined with an on-line mass separator has been utilized to produce a few novel radionuclides, for example, ^{152}Tb ($T_{½}$ = 17.5 h) and ^{149}Tb ($T_{½}$ = 4.1 h), in quantities sufficient for tracer studies [98, 99]. It can lead to a very pure product, but its scope is very limited. As far as nuclear data are concerned, the production cross sections and yields of those radionuclides need to be accurately measured.

2.6.3 Formation of Isomeric States

Most of the commonly used diagnostic and therapeutic radionuclides do not have isomeric states (e.g., ^{11}C, ^{18}F, ^{32}P, ^{89}Sr, ^{123}I, ^{131}I and ^{201}Tl), ^{99m}Tc being an exception. However, many of the novel metallic radionuclides have isomeric states, which may distort the images and cause extra radiation dose to the patient: their check is therefore absolutely necessary. The relative formation of the two isomeric states under consideration is dependent on several factors, among them the spins of the two states concerned, the type and energy of the projectile, and the reaction channel involved. As an example, results for the isomeric pair ^{52m}Mn (21 min)/^{52g}Mn (5.6 d) are shown in Fig. 2.19. The five nuclear processes, viz. ^{52}Cr(p,n), ^{52}Cr(^{3}He,t), ^{54}Fe(d,α), ^{54}Fe(n,t) and ^{54}Fe(^{3}He,αp), all leading to the pair ^{52m,g}Mn, of interest in PET studies, give different isomeric cross-section ratios. At low energies (<10 MeV), the short-lived ^{52m}Mn ($T_{½}$ = 21 min; $I = 2^{+}$) is favoured because of its low spin but at higher energies (>15 MeV) the yield of the longer lived ^{52g}Mn ($T_{½}$ = 5.6 d; $I = 6^{+}$) increases considerably due to its higher spin [100]. In order to avoid ambiguities in PET scans, it is recommended to use the longer lived ^{52g}Mn after the complete decay of ^{52m}Mn.

For other nuclei, such as ^{94m,g}Tc and ^{120m,g}I, on the other hand, the desired radionuclide is either shorter lived or its half-life is comparable to that of the undesired isomer. In those cases, the demands on nuclear data are more stringent. There is then the need to investigate several possible nuclear reactions and choose for production a route that gives the lowest impurity level. For example, the production of ^{94m}Tc was studied in three reactions, namely ^{94}Mo(p,n), ^{93}Nb(^{3}He,2n) and ^{92}Mo(α,d), out of which the ^{94}Mo(p,n)^{94m,g}Tc process led to ^{94m}Tc with the least amount of ^{94g}Tc [101]. Similarly, the production of ^{120g}I was also studied in three reactions, namely ^{120}Te(p,n), ^{120}Te(d,2n) and ^{122}Te(p,3n), out of which the ^{120}Te(p,n)^{120m,g}I process led to ^{120g}I with the least amount of ^{120m}I (cf. Fig. 1 in Appendix V).

In contrast to isomeric states in non-standard positron emitters, an isomeric state within a therapeutic radionuclide may constitute an ideal source of radioactivity

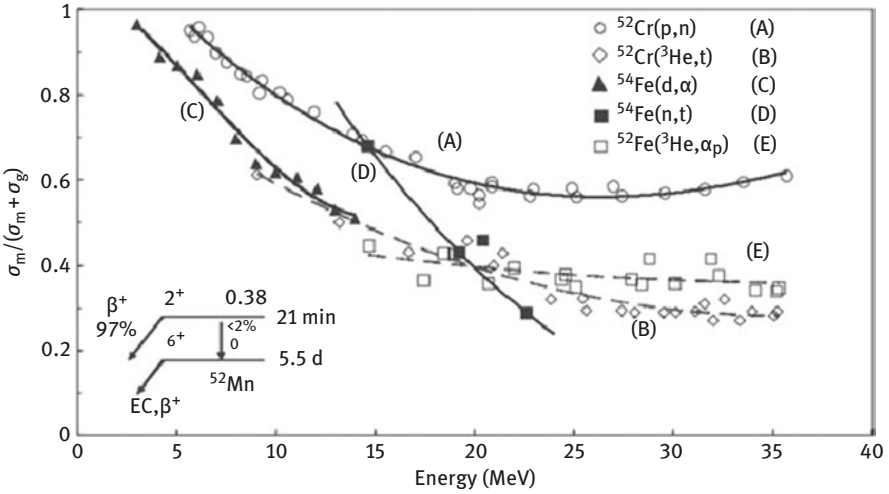

Fig. 2.19: Isomeric cross-section ratio $\sigma_m/(\sigma_m + \sigma_g)$ for the isomeric pair ^{52m}Mn/^{52g}Mn measured as a function of projectile energy in several nuclear reactions, taken from Qaim et al. [100], with courtesy of De Gruyter.

(e.g., ^{117m}Sn, ^{193m}Pt, as discussed earlier). The highly converted internal transition leads to the emission of conversion electrons, Auger electrons and X-rays, which are useful for internal therapy. Hence, studies related to both decay and production data of such isomers will constantly remain part of a radionuclide development programme. As regards their production, the α-particle induced reactions are preferably used (see above) due to the high spins of those isomeric radionuclides.

The study of isomeric states thus constitutes an interesting and challenging problem, both from theoretical and application points of views. On one hand, improvements in nuclear model calculations are needed to describe the isomer ratio and, on the other, for obtaining the desired isomer with high radionuclidic purity, there is a constant need to investigate its novel production routes.

2.7 Photon-Induced Reaction Cross-Section Data

The γ-rays emitted by a ^{60}Co source (1.17 and 1.32 MeV) have found extensive use in external radiation therapy, food preservation and radiation chemistry studies. They only cause atomic and molecular effects, that is, the ionization and excitation phenomena. Due to low energies, a nuclear reaction cannot be induced. The same applies to small electron accelerators, with energies up to about 10 MeV (called betatrons), installed at some hospitals. They deliver hard photons for radiation therapy. Those photon energies are just near the thresholds of photonuclear reactions. So the interest in those reactions, if any, has been more from the

radiation protection point of view rather than for medical radionuclide production. At higher energies, however, the (γ,n) and (γ,p) reactions start gaining significance. In the heavy mass region, photofission is also possible. In recent years, photonuclear reactions have received stronger attention in connection with medical radionuclide production. Several groups are working on development of high-intensity photon sources, especially in the USA, but also in Ukraine and Korea. The electron beam from an accelerator falling on a heavy metal target delivers photons with an energy spectrum extending from about 0.1 MeV to the maximum energy of the electron. Over the energy range up to about 40 MeV, several nuclear reactions can be induced, resulting in the formation of a few medically interesting radionuclides. Some examples are:

^{48}Ti(γ,p)^{47}Sc; ^{68}Zn(γ,p)^{67}Cu, ^{100}Mo(γ,n)^{99}Mo;
^{104}Pd(γ,n)^{103}Pd; ^{124}Xe(γ,n)^{123}Xe → ^{123}I; ^{232}Th(γ,f)^{99}Mo and
^{nat}U(γ,f)^{99}Mo.

The radioactive products formed are among the diagnostic and therapeutic radionuclides discussed earlier.

Nuclear model calculations on medium mass target nuclei show that the threshold of a (γ,n) reaction lies at approximately 8 MeV and the maximum of the excitation function at about 15 MeV, the cross section at the maximum being around 150 mb. The threshold of a (γ,p) reaction in the same mass region lies at approximately 12 MeV, the excitation function has a broad maximum between 20 and 30 MeV, with a cross-section value of about 10 mb. Thus, the (γ,p) reaction is considerably weaker than the (γ,n) reaction. Experimentally, the (γ,n) reaction has been more commonly studied than the (γ,p) reaction. The photonuclear reaction cross sections are available in an IAEA file [102] but the database is weak. Two typical excitation functions are shown later in Section 3.4.2. For medical radionuclide production the (γ,p) reaction is more suitable [103] because it leads to no-carrier-added product. However, due to the low intensities of the presently available accelerators, it is very hard to produce radionuclides in quantities sufficient for medical application. On the other hand, it is believed that the accelerator technology can be developed further to deliver electron beam currents of much higher intensities than in the presently available accelerators. This would compensate for the low cross section and would boost up the batch yield. With further intensification of technological efforts related to development of high-intensity accelerators for medical radionuclide production, the need for accurate photon-induced reaction cross-section data will also increase.

2.8 Concluding Remarks

The role of nuclear data in efficient production and medical application of radionuclides is well established. The data help to meet the quality requirements, that is,

suitability for imaging and minimisation of radioactive isotopic impurities. The status of nuclear data of the commonly used diagnostic and therapeutic radionuclides is generally good, except for some inconsistencies both in decay and production data. Regarding further needs, more information on Auger electron spectra originating from the decay of the presently used diagnostic radionuclides, for example, ^{67}Ga, ^{111}In and ^{123}I, is desired, especially in view of microdosimetry.

The major data needs are associated with the development of novel radionuclides for medical applications or when a new production route of an established radionuclide is searched for. Among the novel radionuclides, presently the emphasis is on non-standard positron emitters for diagnosis and low-range but highly ionizing radiation emitters for internal radionuclide therapy. Regarding the former, both decay and production data need improvement, calling for new measurements, evaluation of existing data and validation of the evaluated data. Regarding the therapeutic radionuclides, the need is more for production data. As far as the search for alternative production routes of an established radionuclide is concerned, attempts to produce ^{99}Mo and ^{99m}Tc provide the best examples: the list of data needs is relatively long.

Medical radionuclides are mostly produced using a research reactor or a cyclotron. In the latter case, generally a small cyclotron is used for the production of positron emitters and a medium-sized cyclotron for SPECT and therapeutic radionuclides. For the production of a few special radionuclides, intermediate energy charged-particle accelerators/cyclotrons are also gaining importance. A newer approach is to develop production routes of a few radionuclides via photonuclear reactions. On a long-term basis, the use of non-conventional fast neutron sources, for example, deuteron breakup neutrons or spallation neutrons, for the production of some therapeutic radionuclides also deserves attention. Thus, new vistas are expected to open up in the future with respect to further development of radionuclide production technology. The supporting nuclear data research will therefore continue to play an important role.

It should be mentioned that this chapter covers the basic principles of nuclear data of medical radionuclides, giving some typical examples of data and their applications. For more extensive information on a particular radionuclide, the user is advised to consult the detailed data files and libraries cited in the text.

3 Irradiation Technology

3.1 General

The basic methodology of medical radionuclide production is the same as of activation cross-section measurement described in Chapter 2, the major difference being in the amount of the induced radioactivity. Whereas in cross-section measurement generally tracer quantities up to ~100 kBq are involved, in radionuclide production for application, several GBq amounts are commonly encountered. A further difference lies in the quality of the radioactive product. Whereas a nuclear reaction cross section can be measured by characterising a certain specific radiation, for example, a γ-ray, of the investigated reaction product, even in a mixture of many activation products, the radionuclide desired for medical application must be free of all isotopic and non-isotopic impurities. This puts a heavy demand on the target material to be used: it should be of well-defined chemical form and of high chemical purity. In special cases, the use of isotopically enriched material is essential to obtain the required radionuclidic purity of the product. Thus, considerable effort is needed to develop a production method based on a known knowledge of nuclear data. The first major effort is to devise a target system for high-intensity irradiation with a projectile (neutron, charged particle or photon). The next step is the chemical processing of the irradiated material. The irradiation technology is described in this chapter and the chemical separation techniques are treated in the next chapter. Due to somewhat different technologies involved in irradiations for radionuclide production at a nuclear reactor or a cyclotron, they are discussed below separately.

3.2 Reactor Irradiations

3.2.1 Solid Targets

For irradiations in nuclear reactors, generally non-corrosive solids with high melting points are used. Liquids and solutions are not used because of the formation of hydrolytic and radiolytic products. The target material should not decompose at an elevated temperature or substantially deteriorate under the impact of radiation. Due to this reason almost all organic materials are excluded as targets for large-scale production of radionuclides. Pure metals or alloys are commonly used as targets, but the dissolution of the material after irradiation and the ease of subsequent chemical processing are important considerations in designing a target system.

In reactor irradiations, generally the target size is not a big problem, provided the whole target is exposed uniformly to the neutron flux. However, for elements with high (n,γ) cross sections, the variation in the neutron flux within the sample

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needs to be taken into account. Furthermore, heat generation has to be considered. Although irradiations with thermal neutrons do not cause much heating, some of the γ-rays emitted in the neutron capture process can be absorbed in the sample, especially if its size is large. In irradiation with fast fission neutrons, larger amount of energy is absorbed in the sample. Efficient cooling is thus essential to avoid overheating and destruction of the target.

The sample for large-scale production of a radionuclide is generally introduced in a high-purity synthetic quartz ampoule, which is then sealed. The use of a pyrex or soda glass ampoule is discouraged because of boron and sodium contents. The $^{10}B(n,\alpha)^{7}Li$ reaction has an exceptionally high cross section (3840 b) even at thermal energies and the emitted charged particles, α and ^{7}Li, deposit considerable amount of energy within the ampoule, thereby increasing the risk of damage of the sample. With regard to sodium, it undergoes activation to ^{24}Na which is a hard γ-ray emitter and causes subsequent problem in the handling of the ampoule. The sealed quartz ampoule containing the sample is placed in an aluminium can, which is then transferred to the interior of the reactor for irradiation in a well-cooled target-holder system. Some activity is produced through the $^{27}Al(n,\gamma)^{28}Al$ ($T_{½}$ = 2.2 min) reaction (σ_{th} = 230 mb) as well as through the $^{27}Al(n,p)^{27}Mg$ ($T_{½}$ = 9.5 min) reaction (σ_{FS} = 4 mb). Their half-lives are, however, short, allowing the handling of the irradiated target soon after it is taken out of the reactor.

The length of an irradiation in a nuclear reactor depends on the cross section of the nuclear process used and the half-life of the product. For the production of ^{153}Sm ($T_{½}$ = 1.93 d) via the $^{152}Sm(n,\gamma)$ reaction, for example, a one-day irradiation may be sufficient, whereas for the production of ^{99}Mo ($T_{½}$ = 2.75 d) via the $^{235}U(n,f)$-process, irradiation times of about 5 days are commonly used. For the production of ^{89}Sr ($T_{½}$ = 50.5 d) via the $^{89}Y(n,p)$ reaction, on the other hand, due to the low cross section (σ_{FS} = 0.31 mb) of the nuclear process, irradiation times of about 50 days are necessary. For irradiations of a few days, samples are generally inserted in and removed from the irradiation position by a hydraulic system, that is, the reactor operation is not disturbed. However, for each irradiation position in a reactor, the heat flux capacity at the surface of the capsule is limited (~100 kW m^{-2}) [cf. 25]. For very long irradiations, other specially designed systems of inserting and removing the samples are used.

3.2.2 Gas Targets

Irradiation of inert gases in reactors has also been utilized to some extent to produce a few special radionuclides, for example, ^{37}Ar ($T_{½}$ = 35.0 d) and ^{79}Kr ($T_{½}$ = 34.9 h), which are of potential industrial interest. They are produced in MBq amounts via the nuclear processes $^{36}Ar(n,\gamma)^{37}Ar$ and $^{78}Kr(n,\gamma)^{79}Kr$, respectively, by irradiating natural or enriched Ar or Kr gases. The same irradiation methodology

has also been used in producing kBq amounts of ^{123}I ($T_{½}$ = 13.2 h) via the $^{124}\mathrm{Xe}(\mathrm{n},2\mathrm{n})^{123}\mathrm{Xe} \xrightarrow[2.1\ h]{EC} {}^{123}\mathrm{I}$ process [cf. 104].

Considerable effort has been devoted to development of gas irradiation technology for large-scale production of the radionuclide ^{125}I ($T_{½}$ = 59.4 d) via the $^{124}\mathrm{Xe}(\mathrm{n},\gamma)^{125}\mathrm{Xe} \xrightarrow[16.9\ h]{EC} {}^{125}\mathrm{I}$ process. It consists of filling an Al capsule with Xe gas up to a pressure of about 5 bar and then sealing it. After extensive tests against leakage, the capsule is placed in an Al can and irradiated in the reactor [26]. Thereafter, the sample is taken out of the reactor and the capsule is cut in a vacuum apparatus. The decay produced radioiodine (^{125}I) is then washed from the inner walls of the capsule and collected in a small volume of dilute alkaline solution. Efforts are underway to prepare capsules of other materials to be able to raise the gas pressure within the capsule up to about 100 bar.

3.2.3 Yields

As mentioned above, the batch yield of a radionuclide achieved in a production run should be as high as possible, compatible with its desired purity. This may amount, for example, in the case of fission produced ^{99}Mo, up to 30 TBq (3×10^{13} Bq). Obviously very advanced remotely controlled/automated technology is needed to handle that level of activity.

Before reaching the maximum level of production of a radionuclide via a chosen nuclear route, it is important to determine the production yields under various chosen conditions. In general, it is found that if a proper target is chosen and the irradiation is done in a well-characterised position in a reactor, the experimental batch yield agrees within about 20 % with the yield calculated theoretically from the irradiation parameters, that is, the mass of the target, the time of irradiation, the cross section of the reaction and the estimated neutron flux. In case of strong flux variation or large uncertainty in the cross section, larger deviations may be observed between the measured and the calculated yields. It may then be necessary to do further optimisation work.

3.3 Cyclotron/Accelerator Irradiations

3.3.1 General Considerations

One of the major efforts in cyclotron/accelerator production of medically important radionuclides consists of development of a suitable target system for irradiations [cf. 105]. Due to use of high beam currents the power density effective at a target could be rather high (up to a few kW cm^{-2}); an efficient heat transfer is thus one of

the prime requirements in target construction. Some other considerations in target design are discussed below.

In principle, several nuclear reactions may have cross sections that are high enough for use in the production of a radionuclide. In the choice of a target material, however, the mechanical and chemical properties of the substance play a very important role. Solids like metals, alloys or oxides, liquids and gases can all be used, provided they can withstand high beam currents, do not lead to radiation induced strong chemical changes, give rise to a high yield of the radionuclide and allow its easy chemical separation.

The chemical reactivity of the product is a paramount importance for subsequent labelling of a molecule with the radionuclide. Often the chemical state of the product radionuclide is determined by the chemical composition of the target filling and the reaction within the target, especially in the case of gaseous target materials. High specific activity of the product is often essential for application in humans. Furthermore, the recovery of the target material is an important consideration while using isotopically enriched targets (see below).

Another important consideration in target design is the projectile energy range to be covered within the target. In general, the specific loss of energy of a projectile in a target increases with its decreasing energy. In practice, it means that although a small amount of the target material may be enough to construct a target for use in a low-energy production reaction, it may be too small for production via an intermediate energy process. As an example, for the production of ^{124}I via the ^{124}Te(p,n)^{124}I reaction over the energy range of E_p = 14 → 10 MeV, about 0.22 g cm^{-2} of the enriched target is needed. For its production via the ^{126}Te(p,3n)^{124}I reaction over the energy range of E_p = 38 → 28 MeV, about 1.15 g cm^{-2} of the enriched target is needed. If the small amount of 0.22 g cm^{-2} used in the (p,n) reaction is also employed in the (p,3n) reaction, the energy range would correspond to E_p = 38 → 36 MeV; thus, the energy absorption would be only 2 MeV and not 4 MeV as in the low-energy range. It is also worth pointing out that if a higher energy beam of protons, for example, 70 MeV, would be put on a Te target of 0.22 g cm^{-2} thickness, the energy absorption would amount to only 1 MeV. The relatively high specific absorption of the low-energy beam renders the production of radionuclides, especially non-standard positron emitters, at low-energy cyclotrons, using small amounts of rather expensive highly enriched materials, very effective. The batch yields achieved, however, are limited. Much higher yields could be obtained using intermediate energy reactions. On the other hand, the amount of the target material needed would then also be much higher. Due to high cost of the isotopically enriched materials, they are seldom used in the production of a radionuclide via an intermediate energy reaction.

A further consideration in medium- to large-scale production of radionuclides using charged particles is the energy, shape and size of the beam. In irradiations using an internal target, the energy is given by the machine parameters and the

beam has generally an elliptical shape. In case of extracted beams, the energy is determined by the TOF or the activation method and the shape is controlled through collimators placed in front of the irradiation target (see Chapter 2). However, in contrast to the work on cross-section measurement, where a low-intensity well-focussed beam is required, for radionuclide production an intense and rather diffused beam is used.

Power Density

The energy generated through the absorption of a charged-particle beam per square centimetre of the target area is called *power density*. A defocused beam reduces the power density effective at the target. Furthermore, if the beam falls not perpendicularly but at a slanting angle on the target, the power density is further reduced. This is illustrated below by a numerical example.

Suppose that a 10 μA beam of 20 MeV protons of diameter 4 mm falls perpendicularly on a target and is completely absorbed. Then

Energy generated = Loss in energy of particle in MeV × intensity in μA s^{-1}

Energy = $1.602 \times 10^{-19} \times 1 \times 10^{6} \times 6.24 \times 10^{12}$ s^{-1} (for 1 MeV, 1 μA p beam)

Energy = 1 Joule s^{-1} = 1 Watt

$$\text{Power density} = \frac{\text{Energy s}^{-1}}{\text{area}}$$

For the above irradiation conditions,

$$\text{Power density} = \frac{10 \times 20}{0.2 \times 0.2 \times \pi} = 1540 \text{ W}$$

Now if the beam diameter is increased to 8 mm, then

$$\text{Power density} = \frac{1540}{0.4 \times 0.4 \times \pi} = 398 \text{ W}$$

Thus, an increase in the beam size drastically reduces the power density and so irradiations with higher beam currents can be performed if a diffused beam is used.

With regard to *beam angle*, the path of incident particles in the material gets longer according to the relation

$$b = \sin\Theta \times a$$

where a is the path length at angle Θ and b the path length at angle 90°.

Since the beam falls on an increased area, the power density decreases. For example, if the beam falls on a target at 20° instead of 90°, then

$$b = \sin 20 \times a$$

$$b = 0.34 \times a \text{ or}$$

$$a = \frac{b}{0.34}$$

that is, the path length would increase by a factor of about 3; as a consequence, the power density would decrease by the same factor.

In practice today, therefore, defocused beams falling perpendicularly on the target as well as slanting beams falling at angles of 15–20° are commonly used. A discussion of various target systems developed is given below.

3.3.2 Solid Targets

Solid material can be irradiated using both internal and extracted beams. The use of an internal beam demands irradiation within a vacuum system of a cyclotron. Materials having high vapour pressure or showing large sputtering effects as a result of irradiation are therefore avoided. Metals, electroplated targets and alloys that have high melting points and good thermal conductivity are preferred. A typical internal target used at the CV28 cyclotron of the Forschungszentrum Jülich [106] to produce ^{77}Br via the ^{75}As(α,2n) reaction is shown in Fig. 3.1 (see also Fig. 3 in Appendix II). A thin layer of Cu_3As alloy was brought on the surface of a wedged Cu backing, which was intensely cooled by running water at the back. The beam fell on the target at a grazing angle of 6.2° and so a 10 μm thick layer of the alloy was sufficient to cover the desired energy range E_α = 26 → 15 MeV for the production of ^{77}Br. Due to the very low angle of the slanting beam, however, the positioning of the beam on the target presented some difficulty. The use of a temperature sensor helped overcome this difficulty. Several hour irradiations with α-particle beams of about 80 μA were routinely done. The main advantages of internal beam irradiations are: (a) higher intensity than in the case of an extracted beam and (b) full use of the maximum available energy by eliminating energy absorption in the intervening window foils. This may be critical in case of very low-energy cyclotrons. On the other hand, the disadvantages are the rather undefined shape of the beam and the risk of vapourisation of the target material within the vacuum system of the cyclotron.

With regard to irradiation of solid targets with extracted charged-particle beams, it should be mentioned that this is the most common methodology for medical radionuclide production at cyclotrons. There is more versatility in working with the extracted beam than with the internal beam. The technology is very well developed. For example, sketches of three typical target systems in use [cf. 107] are given in Fig. 3.2(A–C). In the first system, the target is in a perpendicular position to the beam direction with cooling water flowing through the target base (Fig. 3.2(A)). The solid target material in the form of a thin disk of 13 mm diameter was fixed by a threaded open cap on the top of the holder [cf. 108]; the irradiation thus being done in the vacuum of the beam tube. The second holder design (Fig. 3.2(B)) is

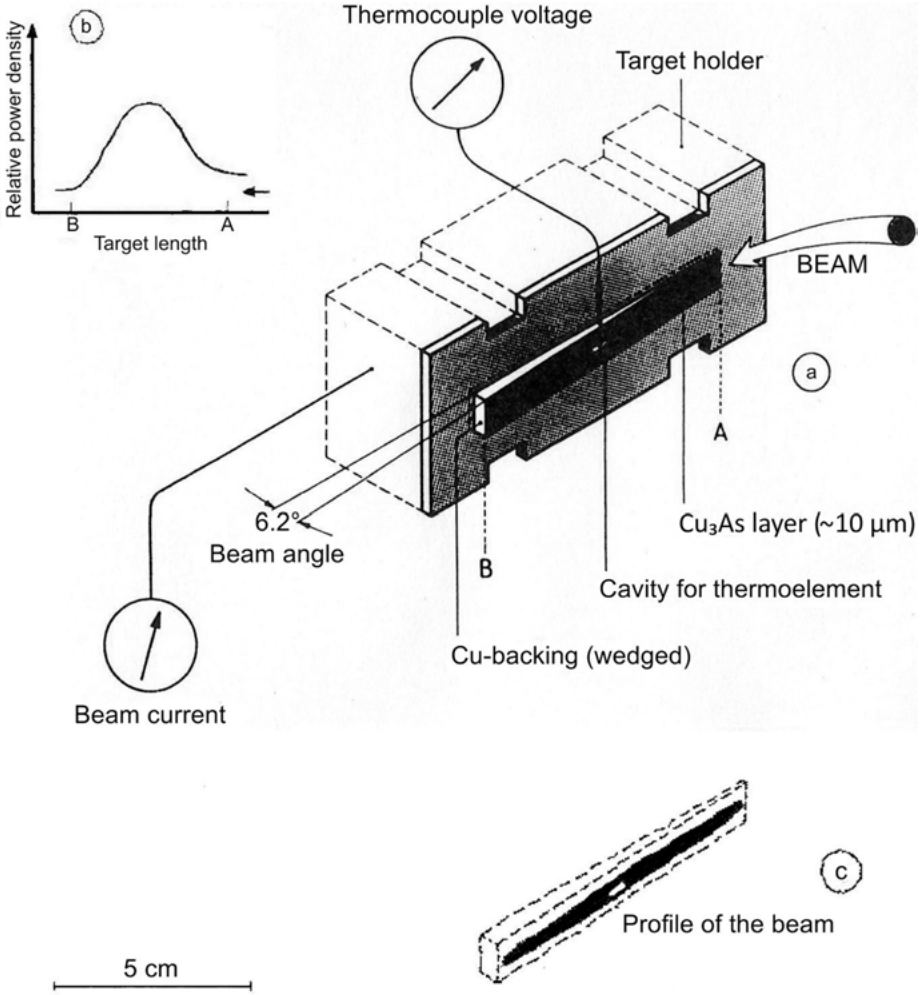

Fig. 3.1: Internal target system at a cyclotron. (A) Thin layer of the target material with high-intensity charged-particle beam falling at a slanting angle of 6.2°. (B) A thermoelement placed in a cavity in the middle of the target allows adjustment of the beam. (C) Beam profile determined by autoradiography. Taken from Blessing and Qaim [106], with permission from Elsevier.

inclined with an angle of 20° relative to the beam [109]. The target material is either electroplated or pressed in a slab of copper with a circular groove of 8 mm diameter and 0.6 mm depth. This slab is soldered to the holder using Sn soldering wire. The charged-particle beam is again directly incident on the target material (see Fig. 2 in Appendix V). After irradiation, this slab is removed from the holder by heating and is subjected to further processing. In one variation of this slanting beam target system, the whole holder is rotated [110, 111]. Furthermore, the incident beam is

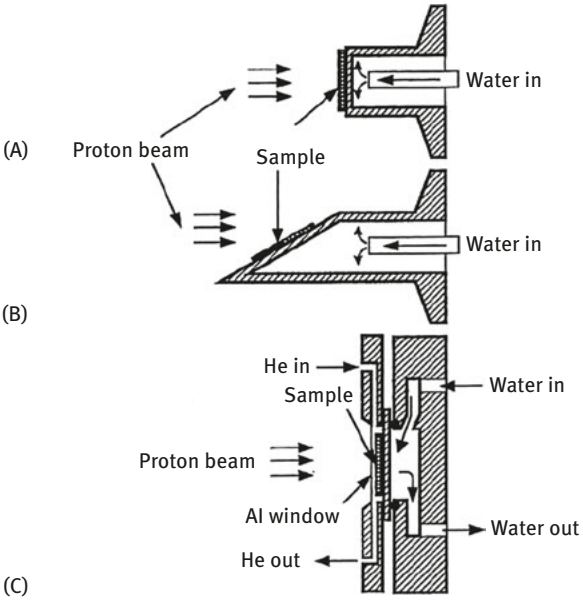

Fig. 3.2: Three typical target holders used in irradiations at a cyclotron: (A) normal target cooled by water at the back, (B) inclined water-cooled target and (C) target cooled in front by He and the back by water. Diagram taken from Hassan et al. [107], with courtesy of De Gruyter.

wobbled. Thus, this combination of a wobbled slanting beam and the rotating target head decreases considerably the effective power density and even metals like Se could be irradiated [110, 111]. In both the variations, only 2π water cooling is done. Depending on the target material, beam currents of up to 10 μA in arrangement (A) and 30 μA in arrangement (B) could be used. In the third arrangement (Fig. 3.2(C)) the cooling is done by water on the backside of the sample and a stream of He gas on its front side [cf. 112]. This system is well suited for materials that could be fixed on a metal base coupled to the holder. A closed-cycle heat exchanger is used to cool the circulating He gas, flowing along the target surface, to 7 °C. Irradiations with beam currents of up to 30 μA could be done.

A further special target system was developed in which 4 π water cooling was applied, that is, flowing water was used both in front and at the back of the target (see Fig. 5 in Appendix II). An open view of such a target is presented in Fig. 3.3. The powder material was pressed to a pellet which was then placed into a groove in a target holder [113] made of aluminium. The groove was closed by a sliding lid. The target was then fitted in the irradiation target head. After irradiation, the target head was remotely opened, and the target holder fell in a lead pot. In the production of ^{123}I via the ^{124}Te(p,2n) reaction on a $^{124}TeO_2$ target, melted on a Pt backing, 22 MeV proton beam of up to 45 μA could be employed. While using a pellet of

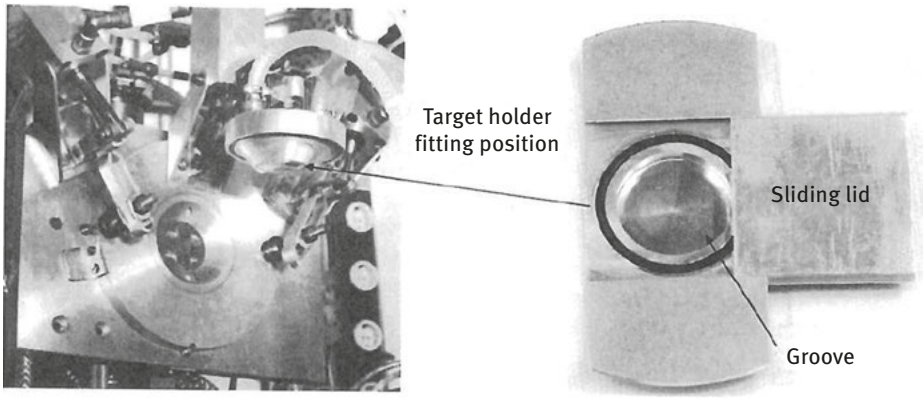

Fig. 3.3: An open view of the 4π water-cooled target head used for irradiation. The Al target holder with a groove for inserting the target pellet is shown on the right, with courtesy of FZ Jülich.

$^{86}SrCO_3$ for the production of ^{86}Y via the $^{86}Sr(p,n)$ reaction, however, a 19 MeV proton beam of only up to 10 μA was applied.

The target systems described above were developed for use at the cyclotron CV28. Because of their versatility, several of them have been recently adapted for irradiations with an extracted beam of 45 or 30 MeV protons available at the Jülich Isochronous Cyclotron (JULIC) and the newly installed IBA CPX 30 cyclotron, respectively, at the Forschungszentrum Jülich.

In recent years a large number of Level III cyclotrons (E < 20 MeV) have been installed at many PET centres. Since at those cyclotrons generally no facility exists for irradiation of solid targets to produce non-standard positron emitters, a few laboratories are building small beamlines to extract the beam and devise suitable target systems. The quality of the extracted beam is generally not good for irradiating small amounts of highly enriched solid material. However, the quality of the beam incident on the target can be improved through careful development work. One such example has been furnished by the installation of a suitable target system at the BC 1710 cyclotron of the Forschungszentrum Jülich [54]. Development work in other laboratories is also being pursued.

In contrast to a low-energy cyclotron, where the rapid loss of projectile energy and the use of small enriched targets demand special ingenuity in target design, at intermediate energy cyclotrons and accelerators the construction of a solid target irradiation device is somewhat easier, because the higher available energy gives more flexibility in the application of more effective heat dissipation methods. Several such systems have been reported from BLIP (Brookhaven), LAMPF (Los Alamos), TRIUMF (Vancouver), iThemba LABS (Cape Town) and INR (Moscow). They are of considerable advantage in the production of some longer lived radionuclides (e.g., $^{68}Ge/^{68}Ga$ and $^{82}Sr/^{82}Rb$

generators). Recently at iThemba LABS, a vertical beam target station has been developed which allows irradiations with 66 MeV protons at nominal beam currents of about 250 μA over extended periods of time. The removal of the heat, however, requires a larger surface in contact with the fast flowing cooling water. The target material is therefore contained in a suitable metal capsule of extended surface area.

Occasionally a series of targets (*tandem mode*) is irradiated. It is then possible to produce two or more radionuclides simultaneously. However, this technique has found only limited application. It was partly used some time ago at TRIUMF. In recent years it has been applied at the iThemba LABS to produce ^{82}Sr and ^{67}Ga, the former using a RbCl target in front to cover the energy range $E_p = 66 \rightarrow 55$ MeV and the latter using an electroplated zinc target over $E_p = 30 \rightarrow 20$ MeV. Similarly two ^{nat}Ag targets in tandem mode have been utilized to produce ^{103}Pd and ^{109}Cd using two chosen energy ranges [114].

In addition to the target systems described above for irradiations of solids, considerable efforts are presently underway to develop new target materials for high-current charged-particle irradiations. In many cases, new alloys and binary compounds are being developed. A few examples are $^{100}Mo_2C$ to produce ^{99m}Tc at St. Louis, $Al_2{}^{124}Te_3$ to produce ^{124}I (at Wisconsin) and NiSe to produce ^{77}Br (at Jülich). Further extensive studies are continuing.

Summarizing this section it should be stated that, although several systems for irradiations of solid targets have been developed, the most common ones in use at Levels II–IV cyclotrons are similar to those given in Fig. 3.2(B) and (C). The system in Fig. 3.2(C), with He cooling in front and water cooling at the back, is commonly used at low-energy cyclotrons to produce non-standard positron emitters via the (p,n) reaction on enriched targets. On the other hand, the system in Fig. 3.2(B) is extensively used in large-scale industrial production of radionuclides, especially if the enriched target material can be electroplated on a metal backing, for example, ^{68}Zn on Au to produce ^{67}Ga via the ^{68}Zn(p,2n) reaction. Under optimised conditions, irradiations with 30 MeV protons of beam currents up to about 800 μA constitute now almost standard technology. The production of radionuclides at intermediate energy cyclotrons and accelerators is presently receiving enhanced attention and optimised irradiation systems are being developed.

3.3.3 Liquid Targets

As mentioned earlier, liquids are never used as target materials in reactor irradiations for radionuclide production. In contrast, liquids are often irradiated with extracted beams from cyclotrons. Originally large-sized water targets of volumes up to 20 mL were used, for example, for the production of ^{18}F via the ^{16}O(^{3}He,p)^{18}F and ^{16}O(α,d)^{18}F reactions with ^{3}He- and α-particles of energies up to 50 MeV. Also flowing loop water targets were employed. In a few cases, molten salt target was

used, especially while producing ^{123}I via the $^{127}I(p,5n)^{123}Xe \xrightarrow{EC} {}^{123}I$ process (for more discussion see Appendix II). After the introduction of the $^{124}Xe(p,x)^{123}Xe \xrightarrow{EC} {}^{123}I$ route, the whole emphasis with regard to ^{123}I production got shifted to gas targetry (see below).

The main problem in liquid targetry was the formation of hydrolytic products. With the introduction of the low-energy nuclear reactions $^{16}O(p,\alpha)^{13}N$ and $^{18}O(p,n)^{18}F$ for the production of ^{13}N and ^{18}F, respectively, combined with the development of high-intensity low-energy cyclotrons (Level III), it became common to utilize water targets for the production of those two radionuclides for PET studies. Since the material needed to cover the optimum energy range for the production of ^{13}N or ^{18}F is small, it proved advantageous to use targets filled with H_2O to generate ^{13}N or with $H_2{}^{18}O$ to produce ^{18}F, both under pressure to avoid radiolysis. In particular for ^{18}F, the constraints of low proton energy and high cost of the highly enriched target material called upon construction of specially designed small-sized targets (for a review of earlier work cf. [115]). Today those small-sized targets are extensively used for large-scale production of ^{18}F.

A typical water target developed at the Forschungszentrum Jülich is shown in Fig. 3.4 [20, 115]. It consists of a titanium body, electron beam welded to two titanium foils (75 µm thick), which act as front and back windows. The target takes 1.3 mL of water with no expansion space and the thickness of the water filling amounts to 3.5 mm. During irradiation, the back window is water-cooled, typically

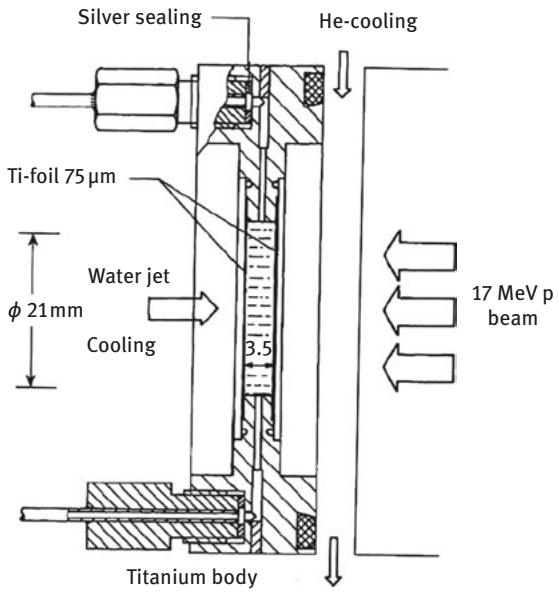

Fig. 3.4: Typical medium-pressure water target system for the production of ^{13}N and ^{18}F at a cyclotron, taken from Stöcklin et al. [20], with courtesy of De Gruyter.

to 10 °C, and the front window is helium-cooled to −7 °C. The target can be remotely loaded with water and evacuated by using a He drive transfer system. The same target can be used for the production of both ^{13}N and ^{18}F. In the former case, natural water ($H_2{}^{16}O$) is used and the proton energy range within the target corresponds to E_p = 16 → 7 MeV. In the latter case, however, enriched water ($H_2{}^{18}O$) is employed and the effective projectile energy range is E_p = 16 → 3 MeV. The target is normally operated at a beam current of about 20 μA of 17 MeV protons. The pressure in a routine production run is about 7 bar. The purity of the ^{18}O-labelled water is of major concern. High chemical purity is absolutely necessary to avoid excessive pressure build-up. For large-scale production, greater than 90% ^{18}O-enrichment is needed to avoid generation of excessive ^{13}N as impurity. Organic impurities must be absent because they may prevent recombination of radiolytically generated oxygen and hydrogen atoms, causing the target to burst. The batch yield of $^{18}F^-$ at the end of a 2 h irradiation amounts to about 75 GBq.

Due to the increasing significance of ^{18}F in PET, several modified designs of high-pressure (> 10 bar) water target have been developed in recent years. They can withstand beam currents of up to about 40 μA. The resulting batch yield of ^{18}F amounts to about 150 GBq. A spherical niobium target [116] proved to be very effective for use at cyclotrons with proton energies above 20 MeV. Industrial scale high-pressure targets are now capable of producing up to about 400 GBq $^{18}F^-$ per batch.

The fact that many of the non-standard positron emitters can be produced via the (p,n) reaction using low-energy cyclotrons (cf. Appendix V and [36]) has given a tremendous impulse to their production at hospital-based cyclotrons. Since generally those cyclotrons have only liquid and gaseous targets (to produce ^{18}F, ^{11}C, ^{15}O, etc.), in recent years a conspicuous development has come up, namely, to utilize an existing or a modified liquid target for irradiating solutions of target isotopes [cf. 117, 118]. Those targets are termed as *solution targets*. The solutions irradiated with protons and the radionuclides produced this way (given in brackets) include calcium nitrate (^{44}Sc), yttrium nitrate (^{89}Zr) and so on. It is, however, necessary to take care of the radiation-induced chemical species [cf. 118]. A clean chemical separation of the product is mandatory. The yield of the desired radionuclide is generally low, but it may be enough for local use.

3.3.4 Gas Targets

General Aspects

In contrast to rather scarce use of gas targets in reactor irradiations, highly sophisticated technology has been developed and is extensively used in irradiations of gaseous targets with charged particles, especially at low-energy cyclotrons (Levels I–III), to produce short-lived positron emitters of light mass elements. Initially, in early

1970s, gas flow targets were constructed. The target holder consisted of a relatively broad and long metal tube (Ø = 5 cm; length = 50 cm) through which a stream of target gas was made to flow. The pressure of the gas was adjusted to provide enough target nuclei in the path of the beam to cover the optimum energy range of the excitation function of the nuclear reaction used (cf. Appendix I). The radioactive gaseous product was continuously led to the laboratory area where some chemical processing was done prior to its use in patient studies [cf. 119]. The concentration of the radioactivity was, however, low for preparing many radiopharmaceuticals.

With the development of PET technology, from late 1970s onwards, a big impetus came to gas targetry. Small target holders were designed for batch mode irradiations of pressurised gases with high-intensity charged-particle beams. This called upon thorough considerations of the following factors and phenomena within the gas filled in a target body:

i) scattering of the beam,
ii) formation of plasma and build-up of high pressure,
iii) heat generation and its efficient dissipation,
iv) chemical fate of the radioactive product,
v) yield, purity and specific activity of the product.

A brief discussion of those aspects is given below.

Scattering

The scattering of a charged-particle beam is more pronounced in a gaseous target than in liquids or solids. This is due to the longer path length of the beam in gases. Thus if the target holder is long and its body is not broad enough, part of the beam in the hind part of the target may not strike the gas but the inner wall of the holder. This loss of the beam would decrease the yield of the radioactive product and deposit considerable extra heat energy on the target wall. For containment of the beam within the gas, therefore, target bodies of conical shape were introduced. In general, the length of the conical body is 10–12 cm, with the diameter of the front part about 1 cm and that of the back part about 3 cm. An added advantage of this shape is that the amount of the gas required for target filling is smaller. In a typical gas target (see Fig. 3 in Appendix V), the beam shape was deduced from optical measurements [120] done when the chamber was filled with 4 bar ^{nat}Kr, and irradiation was done with 14.5 MeV protons at I_p = 10 μA. It was observed that a 6 mm diameter beam in front was broadened to 19 mm at the end of the target.

Formation of Plasma

The interaction of a charged-particle beam with the gas in a target system creates plasma, which moves towards the inner wall of the target body. With the increasing

intensity of the beam, the plasma formation increases and the density of the gas along the beam direction decreases. Consequently the number of the nuclei in the path of the beam becomes smaller and the yield of the product is affected. In a production process, the target is generally filled to pressures of about 20 bar which, under the impact of beam currents of about 30 μA, may rise up to about 30 bar. This increase in pressure is often used as a test of positioning of the beam on the gas.

Heat Generation

The high pressure and formation of plasma cause a severe strain on the window metal foils, separating the target from the cyclotron vacuum. Materials like Al, V, Ti, Ni, Nb and Havar have found extensive use as foils. The target body has to be a good heat conductor, and materials like Al, Ti, Ni, Cu, stainless steel and Inconel have found wide applications. For an efficient dissipation of the heat generated during a high-current irradiation, the target body is cooled by circulating water. The target generally has in front a double window, consisting of two foils, through which cooled He gas flows in a closed loop.

Chemical Form

The chemical form of the radioactive product in a gas target strongly depends on the target body and the filling gas. Under the impact of a high-intensity beam, extensive radiation chemical interactions may take place, leading to a variety of radioactive and non-radioactive chemical products. The presence of additives is often a deciding factor regarding the radiochemical state of the product radionuclide.

Yield and Purity

In a good production method, besides high yield, a low level of radionuclidic impurities is desired. This is achieved via the choice of a suitable nuclear process, the relevant target material and the chemical separation scheme. Furthermore, the level of chemical impurities should also be low. Those impurities are introduced via the reagents used and, to some extent, via radiation induced effects like radiolysis and sputtering from the target body. The inactive impurities may have toxic effects and may also form complexes with the radioactive product, thereby decreasing its chemical reactivity. Whenever high specific activity is demanded, special precautions in target construction are required.

Typical Gas Target Systems

The gas targets could be divided into two systems depending on the possibility of removal of the radioactive product, either directly with the target gas or first its deposition on the inner wall, followed by removal in a second step. A discussion of the two systems is given below.

Direct Removal of Radioactive Product

This system is used in the production of ^{11}C, ^{15}O and partly [^{18}F]fluorine. Extensive work on the production of ^{11}C via the $^{14}N(p,\alpha)^{11}C$ reaction has been done in many laboratories. A typical batch target used at the Forschungszentrum Jülich [20, 115] for the production of ^{11}C via this reaction is reproduced in Fig. 3.5. It consists of a conical cylinder made of aluminium–magnesium alloy containing 3% magnesium ($AlMg_3$). The target is 144 mm long, with front and rear parts having diameters of 18 and 44 mm, respectively. The double window in front of the target consists of a 0.6 mm thick aluminium sheet (closing the target) and a 50 μm thick aluminium foil (separating the cyclotron vacuum). A helium stream (0.8 bar, −7 °C) flows through the two foils and cools the window. The target body is cooled by flowing water. The target filling and evacuation systems are also shown. It is filled with high-purity nitrogen gas to a pressure of 12 bar. In a typical production run at 30 μA the pressure rises to 16 bar. The proton energy range within the gas corresponds to $E_p = 13 \rightarrow 3$ MeV. While using "pure nitrogen" containing traces of oxygen as target gas, both [^{11}C]carbon monoxide and [^{11}C]carbon dioxide are formed. Furthermore, some ^{13}N is also formed via the $^{14}N(p,pn)^{13}N$ reaction. Experience has shown that after a high-current irradiation of about 40 min, the ^{11}C formed exists mostly as [^{11}C]carbon dioxide and the amount of ^{13}N is small. After the irradiation, the pressure valve of the target is opened to release the target gas and He (at 0.3 bar) is used to flush the target. The gas stream is then led in a metal tubing (stainless steel, small diameter) to a synthesis apparatus placed in a hot cell. The recovery yield of the radioactivity is >90%.

The above described target system is adapted and also used for ^{15}O production via the $^{14}N(d,n)^{15}O$ reaction. The target is generally filled with high-purity nitrogen gas containing 0.2% oxygen. Irradiation is done with deuterons and the energy range within the gas corresponds to $E_d = 8 \rightarrow 0$ MeV. This energy minimises the production of the longer lived radionuclidic impurities ^{13}N ($T_{½}$ = 10.0 min) and ^{11}C ($T_{½}$ = 20.4 min) generated by the $^{14}N(d,t)^{13}N$ (threshold energy: 4.9 MeV) and $^{14}N(d,\alpha n)^{11}C$ (threshold energy: 5.8 MeV) reactions, respectively (see Chapter 2, Section 2.5.2). A 5 min irradiation with a nominal deuteron beam of 30 μA was found to be sufficient. The gas stream is led in a stainless steel tubing to a hot cell where synthesis of ^{15}O-labelled molecules, for example, [^{15}O]H_2O and *n*-[^{15}O]butanol is done. The recovery yield of the radioactivity is >90%. It may be mentioned that, besides the batch target described here, some gas flow targets are still extensively used for the production of ^{15}O in other chemical forms, such as [^{15}O]oxygen, [^{15}O]carbon monoxide and [^{15}O]carbon dioxide. In each case the radioactivity is carried out of the target with the gas stream.

With regard to [^{18}F]fluorine production, the reaction $^{20}Ne(d,\alpha)^{18}F$ is utilized. Extensive work on targetry and radionuclide removal has been done in many laboratories. A typical target is of conical shape [cf. 56], about 100 mm long, made of Ni, with a He-cooled double window in front. It is filled with Ne gas containing 0.18% F_2

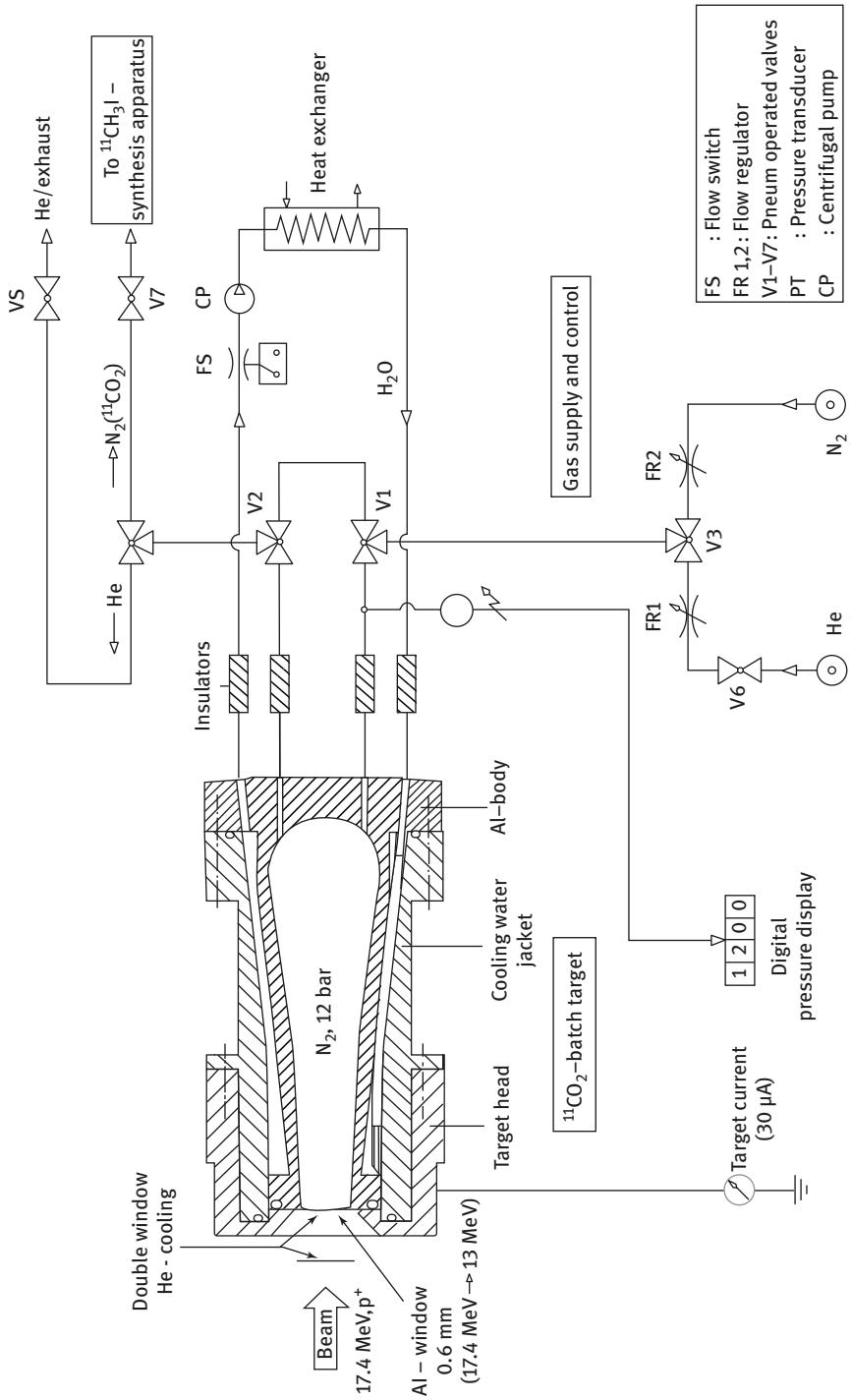

Fig. 3.5: Typical gas target system used in batch mode for production of ^{11}C and ^{15}O at a cyclotron, taken from Stöcklin et al. [20], with courtesy of De Gruyter.

to a pressure of 18 bar. On irradiation for about 2 h with 14 MeV deuterons at a beam current of about 25 μA the pressure rises to 28 bar. At the end of the irradiation, the pressure valve of the target is released and the target gas with the radioactivity is led through a Cu tube to a lead cell for synthesis work. The main factor determining the [^{18}F]fluorine recovery is the chemical state of the target surface. Passivation (pre-fluorination) of the target inner surface is necessary before performing the irradiation to avoid losses of ^{18}F through adsorption on the inner wall. Under optimised conditions, about 75% of the ^{18}F can be recovered in a production run.

Removal of Deposited Radioactive Product

In irradiations of inert gases with light mass charged particles, generally radiohalogens, alkali metals or alkaline earth metals are formed. They are all deposited on the inner walls of the target body. In order to remove them from the walls and to recover them for subsequent use in radiopharmaceutical production, two techniques have been developed. The first one applies specifically to the recovery of [^{18}F]fluorine through a second irradiation, and the second one, involving the rinsing of the target walls with water, is of more universal application.

a) Recovery of [^{18}F]fluorine

The technique of two-step electrophilic ^{18}F production via the ^{18}O(p,n)^{18}F reaction was developed at Wisconsin and Los Angeles, USA. An optimised target and recovery system used at the Forschungszentrum Jülich [121] is reproduced in Fig. 3.6. The target body has a conical shape with front and back radii of 8 and 10 mm, respectively, and a length of 122 mm. The dimensions correspond to the beam shape, which was calculated by Monte Carlo simulation. In this way any interactions between the beam and the wall are avoided and the entire beam is utilized for the nuclear reaction. A hemispherical entrance window with a wall thickness of 500 μm is used instead of the usual double window. The target body including the window is made of an aluminium alloy containing 3% magnesium ($AlMg_3$). The target chamber is cooled with 20 °C circulating water. The window is separately cooled by 6 °C water.

In the first irradiation, the target was filled with 97% $^{18}O_2$ to a pressure of 12.8 bar. On irradiation with 16 MeV protons at 25 μA, the pressure rose to 25 bar. At the end of the irradiation, the gas was cryogenically trapped on molecular sieve into a stainless steel reservoir. For the subsequent recovery of ^{18}F deposited on the inner wall, the target was filled with a 0.8% fluorine/krypton mixture to 10.3 bar and irradiation was done for 15 min with 16 MeV protons at 20 μA. At the end of the second irradiation, that is, the activation step, the [^{18}F]fluorine/krypton gas was transferred via a 60 m long, 3 mm Ø, Cu-tube to the chemical laboratory area to perform labelling reactions. Similar to the Ni target used for the production of [^{18}F]fluorine via the ^{20}Ne(d,α)^{18}F reaction described above, also for the present target a daily passivation of the internal surface is necessary to obtain

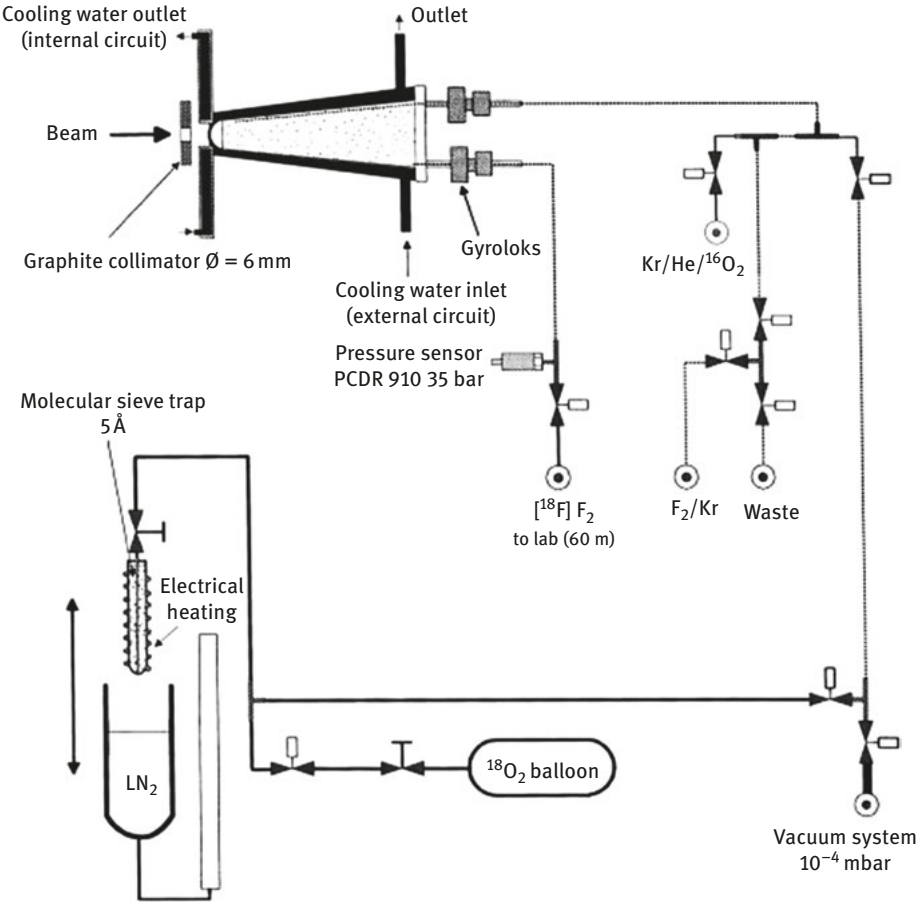

Fig. 3.6: Scheme of the manifold used for handling the highly enriched $^{18}O_2$ gas as target in the production of electrophilic ^{18}F via the $^{18}O(p,n)^{18}F$ reaction, taken from Hess et al. [121], with permission from Elsevier.

a reproducible [^{18}F]fluorine yield. Under optimised conditions, the recovery yield of [^{18}F]fluorine was estimated to be about 70%.

b) Recovery by rinsing the inner wall

The technique of rinsing the inner wall of the target body to remove the deposited radionuclide is common and has been used in several variations. In the simplest form, after the end of the irradiation, at first the target gas is removed, and then sufficient amount of water (or other solvent) is introduced in the target body and, after some shaking, the solution is sucked out of the target. The total volume of the collected solution is generally large (~ 20 mL) [cf. 57].

In an improved version, a conical-shaped cylinder was placed inside the target, which could be rotated using an electrical drive motor. The radionuclide produced during the irradiation got adhered to the inner wall of the conical cylinder. After the end of the irradiation, the target was evacuated, about 5 mL of water was sucked inside the conical cylinder, which was then rotated. After a 5 min rinsing the water containing the radionuclide was pressed out by Ne gas. This methodology was used in the production of $^{18}F_{aq}$ via the nuclear process $^{20}Ne(d,\alpha)^{18}F$ [56]. The removal yield of the product was found to be between 60% and 70%.

Another elegant method developed for the removal of rubidium radionuclides from a Kr target [120] made use of steam (see Fig. 3 in Appendix V). The conical-shaped target body is made of stainless steel (length: 12 cm; front Ø = 1.2 cm; back Ø = 3.0 cm) and it has in front a standard double window He cooling arrangement. For the production of ^{82m}Rb via the $^{82}Kr(p,n)^{82m}Rb$ reaction, > 95% enriched ^{82}Kr gas was filled in the evacuated target up to a pressure of 3 bar and then irradiation was done with 15 MeV protons at a beam current of 20 μA. After the end of the irradiation, the target gas was removed from the target and collected cryogenically in the reservoir. Steam under pressure (at 500 °C) was then introduced into the target and, on cooling, it dissolved some ^{82m}Rb adsorbed on the inner wall of the target. The water droplet was then sucked out of the target. This process was repeated seven times till most of the ^{82m}Rb formed was collected in about 0.5 mL of water. The removal yield of the radionuclide was found to be > 95%.

It should be noted that besides clinical scale production of ^{82m}Rb, the above mentioned technology was also used in tracer level production of ^{75}Br via the $^{78}Kr(p,\alpha)^{75}Br$ reaction. Furthermore, using a still more advanced methodology, particularly with regard to the safe handling of the highly expensive enriched ^{124}Xe gas as target material, the technology has been fully developed at Karlsruhe and Vancouver for large-scale production of the important SPECT-radionuclide ^{123}I via the $^{124}Xe(p,x)^{123}I$ process at a medium-sized cyclotron. Further work on improvement of gas targets, especially those employing highly enriched gases as target materials, is continuing. The major aims are to decrease the leakage of the gas and to improve the recovery of the product.

3.3.5 Production Yields

The integral yield of a radionuclide calculated from the excitation function represents the maximum yield, which can be expected via the nuclear process used. In practice, the experimentally obtained yields in high-current production runs are invariably lower than the theoretical values. The experimental batch yield generally increases with the increasing current. However, the normalised production yield per μA current decreases as a function of the integrated current, presumably due to some loss of the beam in wobbling, due to inhomogeneity in the incident beam as

well as radiation damage effects. Although not many detailed systematic yield measurements have been performed under standardised conditions as a function of increasing beam current, some trends in relative experimental yields for three types of target materials (solid, liquid, gaseous) were ascertained [cf. 105]. Due to different target thicknesses (energy ranges), a quantitative comparison was not admissible. However, qualitatively it was found that the yield decreases rapidly in the case of a gaseous or liquid target. In the former case, it is presumably due to density reduction along the beam direction and, in the latter, due to local boiling and bubble formation [cf. 122]. The experimental yields thus reflect a cumulative effect of the specific conditions prevalent during the production process. Establishing the optimisation parameters of a production process is thus of critical importance in achieving reproducible yields of a radionuclide in charged-particle irradiations. In recent years, considerable progress has been achieved in beam positioning through Monte Carlo simulation calculations, for example, using the codes FLUKA or MCNPX, and more efficient heat dissipation methods have been developed. Nonetheless, experimental yields nearing the theoretical values are not reached. Thus, a constant vigilance on irradiation conditions is mandatory.

A consideration of batch yields of all commonly used cyclotron radionuclides suggests that they lie between 50 and 400 GBq. Those quantities are sufficient for most of the patient care studies, but are often much lower than those encountered in reactor production of radionuclides (see section 1.3.3). Thus, there is always room for further improvement.

3.4 Other Irradiation Systems

Besides the use of nuclear reactors and cyclotrons in medical radionuclide production, presently two other irradiation systems are also finding increasing interest. Although both the systems have been known for more than 50 years, their possible use in medical radionuclide production has been gaining enhanced attention only in recent years. They include the use of (a) fast neutrons other than those from radionuclidic sources and nuclear reactors described above and (b) high-energy photons mentioned above. A brief discussion of the irradiation possibilities is given below.

3.4.1 Deuteron Breakup Neutrons, Spallation Neutrons and White Neutron Sources

Neutrons produced by breakup of 30–50 MeV deuterons on Be have been extensively used in neutron therapy and nuclear reaction cross-section measurements. Because of the forward-peaked nature of the neutron spectrum, the irradiation is done mostly in the 0° direction. A schematic arrangement for irradiations with breakup neutrons at the JULIC and CV28 cyclotrons of the Forschungszentrum Jülich [123] is shown in

Fig. 3.7(A) and the neutron spectrum, characterised by the multiple-foil activation and spectrum unfolding technique, for 30 MeV deuterons on Be, is reproduced in Fig. 3.7 (B). Extensive integral cross-section measurements were done at Jülich using 14 MeV d(Be) neutrons [43, 124] as well as 30 MeV and 53 MeV d(Be) neutrons [125–127]. It was found that the cross sections for the formation of many radionuclides via (n,p) and (n,np) reactions are much higher than those with reactor neutrons.

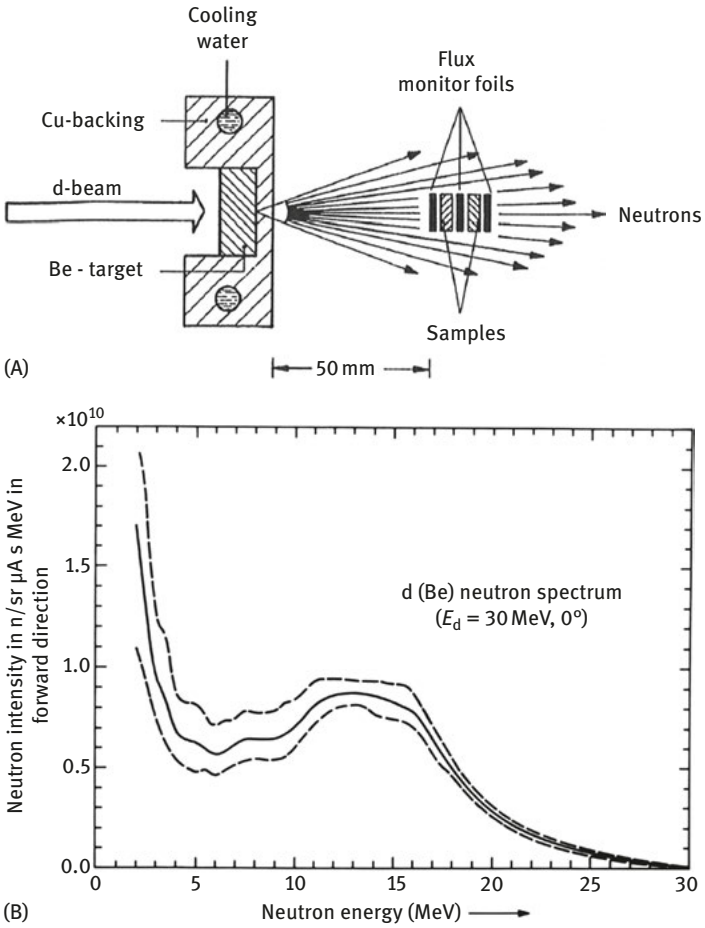

Fig. 3.7: (A) Arrangement for irradiations with deuteron/beryllium breakup neutrons. (B) Neutron flux distribution for 30 MeV deuterons on Be, taken from Wölfle et al. [125], with permission from Elsevier.

At low deuteron beam currents, the neutron irradiations were done in air. For radionuclide production, however, intense deuteron beams would have to be used,

necessitating thereby the construction of a well-cooled Be target, and the irradiation sample would also have to be cooled and placed in a closed system. In recent years attempts have been made at JAERI Tokai to produce ^{67}Cu and a few other radionuclides using breakup of deuterons on a graphite target rather than on a Be target [128, 129]. A high-current target system is being developed.

Besides deuteron breakup neutrons, spallation-type neutrons have also been used in some preliminary investigations on production possibilities of a few radionuclides [130, 131], mainly via the (n,p) reaction. Similarly some thoughts are also developing on the use of white neutron sources produced at high-intensity electron linear accelerators (LINACs) with energies of about 50 MeV. Their use would presumably be more in utilizing the (n,γ) reaction (i.e., as a substitute of a nuclear reactor). However, to date irradiations for practical radionuclide production using a spallation neutron source or a white neutron source have not been reported.

3.4.2 High Energy Photons

As mentioned in Chapter 2, considerable interest has arisen in recent years to produce a few special radionuclides via photonuclear reactions. Enhanced efforts are therefore underway to develop high-power electron linear accelerators (LINACs) to be able to supply intense photon beams. A typical irradiation geometry to produce a radionuclide via a photonuclear reaction is shown in Fig. 3.8(A). The electron beam from an accelerator falling on a heavy metal target delivers photons. The calculated photon spectrum for 40 MeV electrons is shown in Fig. 3.8(B) [cf. 103, 132]. In the same diagram, the excitation functions of the ^{48}Ti(γ,p)^{47}Sc and ^{100}Mo(γ,n)^{99}Mo reactions, taken from Ref. [102], are also shown. Obviously the photon spectrum is suitable for the production of both ^{47}Sc and ^{99}Mo, but extensive development work is necessary to achieve production yields sufficient for medical applications (for more discussion see Chapter 6).

3.5 Concluding Remarks

In this chapter the principles of sample irradiation technology at various facilities have been discussed. Evidently the technology is more demanding in the case of charged-particle irradiations than in neutron irradiations. In particular, the use of highly expensive isotopically enriched material at low-energy charged-particle machines calls upon ingenuous methods for optimum utilization of the beam and safe handling of the material. Also the use of liquids and gases as target materials is very demanding. Some examples of those systems have been presented. Extensive studies continue worldwide, both on target design and target materials. On the other hand, the handling of much larger amounts of radioactivity in reactor irradiations than in

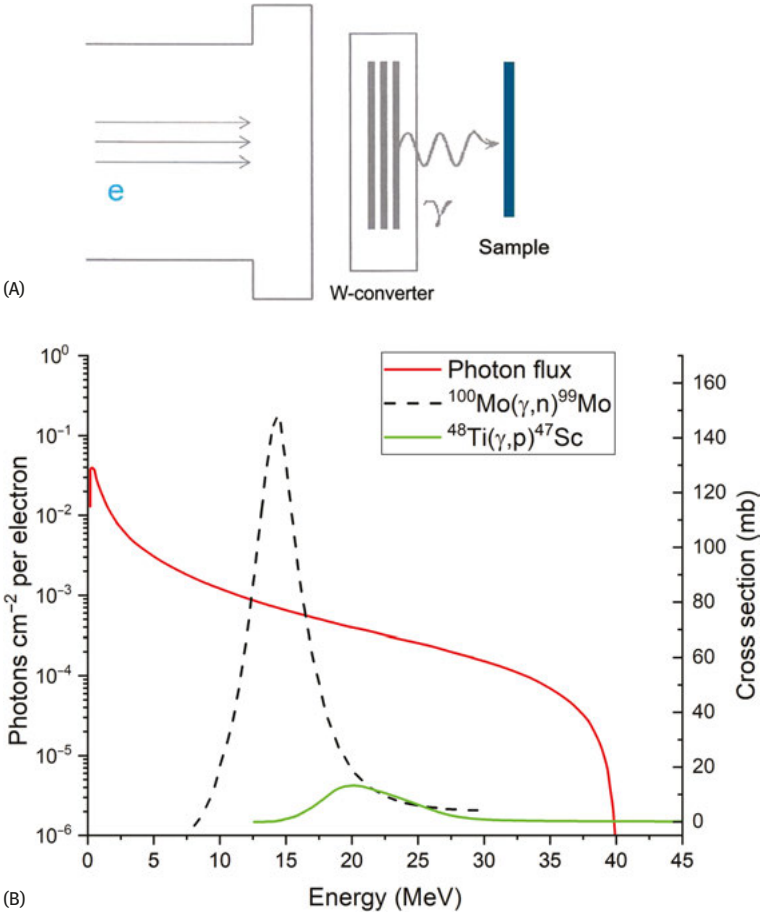

Fig. 3.8: (A) Photon production by impinging a beam of high-energy electrons on a W target. (B) Bremsstrahlung spectrum from 40 MeV electrons on W, taken from Mamtimin et al. [103], with permission from Elsevier. The excitation functions of the reactions ^{100}Mo(γ,n)^{99}Mo and ^{48}Ti(γ,p)^{47}Sc shown in the diagram, are based on the cross-section values given in the data file [102].

cyclotron irradiations demands high-class radiation shielding and sample transport technology. Continuous research and development work is therefore underway with regard to irradiation facilities, as is evidenced by the series of conferences and workshops on targetry and isotopes. For the latest developments in technology, the reader is referred to the proceedings of those conferences. Similarly for more detailed information on industrially established technologies, it is advisable to consult the information supplied by various commercial organizations.

4 Chemical Processing and Quality Assurance

4.1 General Considerations

The chemical processing of an irradiated target material, called *radiochemical processing*, is similar to normal chemical analysis, except for two distinct differences:

a) the radioactive product may exist in the form of several chemical species,
b) the amount of the radioactive product is very small.

The formation of various chemical species occurs due to radiation-induced chemical reactions and nuclear recoil effects. Those effects are more pronounced in gaseous and liquid targets. In a nitrogen gas target for the production of ^{11}C via the $^{14}N(p,\alpha)^{11}C$ reaction, for example, the product radionuclide occurs as $^{11}CO_2$ or ^{11}CO, depending on the target filling, the beam current used and the time of irradiation. Similarly in a water target for the production of ^{13}N via the $^{16}O(p,\alpha)^{13}N$ reaction, the radioactive product could occur as $^{13}NO_2^-$ or $^{13}NO_3^-$, depending on the radiation dose effective in the target. Also in solid targets, the radioactive product may exist in several oxidation states. For example, ^{124}I produced in a $^{124}TeO_2$ target via the (p,n) reaction, or ^{131}I formed in a $^{nat}TeO_2$ target through the $^{130}Te(n,\gamma)^{131m,g}Te \xrightarrow{\beta^-} {}^{131}I$ process, may exist as I^-, IO_3^- or IO_4^-. The chemical processing to be applied must therefore take all these aspects in consideration. Often an oxidation/reduction cycle is necessary to convert the desired radioactive product to one species before performing the radiochemical separation.

The small amounts of radioactive products to be handled after an irradiation are typical of radiochemical work. As is well known, in a nuclear reaction only a very small part of the target isotope is converted into an activated product. In a 1 g target sample, for example, after irradiation the total quantity of the radioactive product may amount to between 10^{-9} and 10^{-12} g (often termed as *tracer quantity*). If the activation process involves an (n,γ) reaction, the product radionuclide and the target nuclide are isotopes of the same element, and a chemical separation is generally not possible. Consequently the specific activity achieved is small. If, however, another nuclear reaction occurs, for example, (n,p) or (p,n), the activated product is again in a small quantity, but it is of a different element and can therefore be chemically separated. Though processing of sub-nanograms of materials is a challenge, yet it is often absolutely necessary to achieve high specific activity of the radioactive product for medical application. Several difficulties may be encountered while dealing with tracer quantities of a material, such as loss of radioactivity via adsorption on glass walls, radiocolloid or aerosol formation. It is therefore advisable to use quartz or teflon, instead of glass, and the highest purity reagents and gases available.

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There are two major aims of chemical processing:

i) to isolate the desired radionuclide in a pure form,
ii) to recover the isotopically enriched target material for reuse.

Although the latter aim is more of economic interest, and is often of great importance in the production of radionuclides at low- and medium-sized cyclotrons (Levels II –IV), the first aim, that is, achieving a high purity of the desired product, is of absolute necessity for medical application. A few other factors related to a good radiochemical separation are: high yield, fast speed, reproducibility of results, simplicity of the procedure, and adaptability to remote control and/or automation. The speed of separation is critical for short-lived radionuclides and the adaptability of the developed separation procedure to remotely controlled/automated processing of highly radioactive targets in a lead cell is of paramount importance from the radiation protection point of view. A further demand is that the highly purified radioactive product has to be made available in a small volume of the final solution (~0.3 mL). Finally it has to meet certain quality assurance criteria before it could be used in further synthetic radiopharmaceutical work. Thus the chemical processing of the irradiated material for medical application demands special expertise in analytical radiochemistry. The separation procedures are discussed in Section 4.2 and the quality assurance methods in Section 4.3.

4.2 Chemical Separation Procedures

Radiochemical separations have been extensively used in fundamental studies on nuclear reactions, where the product radioactivity is low. In medical radionuclide production, however, because of special demands mentioned above, only those methods are interesting that can be applied to large-scale or at least clinical-scale production of the radionuclide. In general, both on-line and off-line methods have been applied. A brief discussion of the two methodologies is given below.

4.2.1 On-line Method of Separation

This method is mostly applied in cases where the radionuclide produced or its precursor is in gaseous form. It has been extensively used in the production of the short-lived radionuclides ^{11}C ($T_{½}$ = 20.4 min) and ^{15}O ($T_{½}$ = 2.0 min), both using a flow or batch target filled with N_2 gas. For production of ^{11}C, the irradiation is done with protons and for ^{15}O with deuterons. The radionuclide coming out of the target in the gas stream is then subjected to chemical processing for converting it to the desired chemical form. The removal of [^{18}F]fluorine formed via the $^{20}Ne(d,\alpha)^{18}F$ reaction in a gas target filled with Ne and 0.18% F_2 is also based on the same principle. On-line

removal of the gaseous products from solid targets has also been applied, for example, in the production of ^{123}I via the $^{127}I(p,5n)^{123}Xe \xrightarrow{EC} {}^{123}I$ process. On irradiation, the target material NaI gets melted within the target. A stream of He gas is then led through the molten system, whereby ^{123}Xe formed is carried out of the target with the He stream. It is then cryogenically separated from He and used for the recovery of ^{123}I (see Fig. 8 in Appendix II). Some success was also achieved with respect to on-line removal of ^{94m}Tc from a molten enriched $^{94}MoO_3$ target being irradiated with 11 MeV protons to induce the (p,n) reaction. Another example is the removal of ^{77}Kr by a He stream from a NaBr target during irradiation with 60 MeV deuterons, whereby ^{77}Kr is formed via the ^{79}Br(d,4n)-process. After removal, ^{77}Kr is trapped in a vessel cooled by liquid nitrogen. It is then used as a precursor for ^{77}Br production (see Appendix II).

A yet another on-line system of removal of radioactivity from a target involves the use of two irradiations, for example, in the production of [^{18}F]fluorine via the ^{18}O(p,n)^{18}F reaction in a gas target filled with highly enriched $^{18}O_2$. As mentioned in Chapter 3, the primary irradiation leads to the formation of the no-carrier-added product ^{18}F, which gets adsorbed on the inner wall of the target body. After cryogenic removal of $^{18}O_2$, the target is filled with Kr containing 0.8% F_2, and the second short activation irradiation is carried out. The [^{18}F]fluorine is then removed from the target vessel with the outgoing gas stream. Furthermore, the removal of radioactivity adsorbed on the inner wall of a gas target (after irradiation) by rinsing the wall with water or introducing steam and collecting the wash solution (see Chapter 3) may be regarded as a special form of on-line separation of the product.

Besides on-line separations from gaseous and molten targets described above, the isolation of no-carrier-added ^{18}F activity formed via the ^{18}O(p,n)^{18}F reaction in a $H_2{}^{18}O$ target constitutes a very special form of on-line separation. The irradiated water is transferred from the target to the hot cell through a polypropylene tube (Ø = 0.8 mm) and led to an ion-exchange resin (carbonate form) column. The radionuclide ^{18}F is adsorbed on the column, whereas the ^{18}O-enriched water flows through and is recovered for reuse. Later ^{18}F is removed from the column for further chemical processing.

4.2.2 Off-line Methods of Separation

As discussed in Chapter 3, most of the irradiations for radionuclide production, both in reactors and at cyclotrons, are carried out using solid targets. A large number of dry and wet chemical processing methods have been developed to separate the desired radionuclides in no-carrier-added form from macroamounts of inactive material and strong matrix activities. Some of the commonly used methods are discussed below.

Distillation

This method makes use of the volatility of certain elements or their chemical compounds and the separation is based on differences in vapour pressures. The conversion of a non-volatile element to a volatile form is achieved through adjustment of experimental conditions. Both dry and wet distillation methods have been used.

The technique is applicable at both macro- and tracer levels. In the latter case, the use of a non-isotopic carrier is needed. An example of the removal of a volatile rare gas is furnished by the production of ^{77}Kr via the ^{77}Se(^{3}He,3n) reaction [110]. A thin layer of ^{77}Se metal on an Al plate was irradiated with ^{3}He–particles at a slanting angle of 20°. The radioactive ^{77}Kr produced remained trapped in the target. After the irradiation, the target was placed in a degassing apparatus, a stream of He was led through the apparatus and heating was started. Radiokrypton was swept through and adsorbed on a molecular sieve in a stainless steel trap cooled with liquid nitrogen. The product was found to be quite pure and could be directly used in inhalation studies.

The dry distillation method finds extensive use in the removal of radioiodine from a tellurium dioxide target. It has been applied in the reactor production of ^{131}I through the $^{130}\mathrm{Te}(\mathrm{n},\gamma)^{131\mathrm{m,g}}\mathrm{Te} \xrightarrow{\beta^-} {}^{131}\mathrm{I}$ process on a $^{\mathrm{nat}}TeO_2$ target as well as in the cyclotron production of ^{120}I, ^{123}I or ^{124}I via the (p,n) reaction on the respective enriched target $^{120}TeO_2$, $^{123}TeO_2$ or $^{124}TeO_2$. The apparatus used earlier (see Fig. 6 in Appendix II) has been updated and the presently used version [112] is shown in Fig. 4.1. The distillation tube is made of quartz (Ø = 3.9 cm, length = 30 cm) and is placed in an

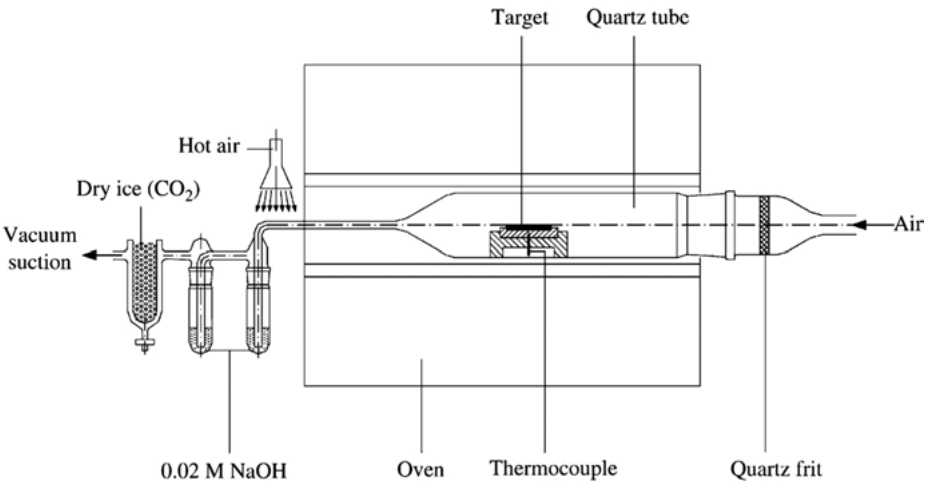

Fig. 4.1: Simplified sketch of quartz distillation apparatus for the separation of radioiodine (^{120}I, ^{123}I or ^{124}I) from irradiated $^{120}TeO_2$, $^{123}TeO_2$ or $^{124}TeO_2$ target, respectively. The tube area outside the oven is heated by a stream of hot air. Taken from Qaim et al. [112], with permission from Elsevier.

oven. It is connected on one side with a row of traps (two containing about 0.5 mL of 0.02 M NaOH solution each, and the third one solid CO_2) and a vacuum pump. The other end is open for introducing the irradiated target that consists of tellurium dioxide on a platinum backing. A vacuum suction allows air to flow through the tube gently. The oven is warmed up to 750 °C in steps and maintained at that temperature for about 15 min. The radioiodine released is carried with the air stream and is deposited mainly in the first trap (>98%); a small fraction is found in the second trap (<2%). The overall distillation yield was found to be about 90%.

It should be mentioned that the exact mechanism of radioiodine removal from the target is not known, but presumably it involves the formation of high oxides of iodine that are volatile and get decomposed immediately when they come in contact with the solution in the first trap. Optimisation experiments showed that the distillation temperature should lie above the m.p. of TeO_2 (733 °C) but should not be too high to avoid Te loss. Since on melting, the radiation damage effects are healed out, the enriched tellurium dioxide target can be reused without applying any further target recovery process.

Besides the dry distillation method used for the separation of rare gases and radioiodine, radionuclides of many other elements produced in various matrices are separated by the conventional dry or wet distillation method. The irradiated target element is treated with a gas or is dissolved in a suitable medium, so that the radionuclide is converted to a volatile chemical form, and is distilled over to another vessel. A few general examples of separations via distillation are given below:

- as oxide (OsO_4, RuO_4, Re_2O_7, Tc_2O_7),
- as chloride ($GeCl_4$, $AsCl_3$, $SeCl_4$, $ZrCl_4$),
- as hydride (SbH_3, PH_3, AsH_3, etc.).

Some typical examples of separations based on distillation applied in the production of medical radionuclides are:

- Separation of ^{211}At formed via the ^{209}Bi(α,2n)^{211}At reaction. The standard procedure used involves distillation at 650 °C in a quartz oven. A stream of dry nitrogen, argon or oxygen carries ^{211}At out of the distillation apparatus, which is then trapped in a cooled vessel. Thereafter astatine is dissolved in a small volume of an organic solvent.
- Separation of ^{131}I from a Te metal target irradiated in a nuclear reactor. The target is treated in a distillation flask with a mixture of chromic acid and sulfuric acid, heated and refluxed. After addition of some oxalic acid, the flask is again heated and the radioiodine distilled over is collected in a receiver containing about 10 mL of 0.01 M Na_2SO_3 solution.
- Separation of ^{30}P formed via the ^{27}Al(α,n)^{30}P reaction. The irradiated target was transferred to a distillation flask containing NaOH solution. On dissolution of Al the nascent H converted ^{30}P to phosphine, which was swept off by He gas. The gas stream was then led through a liquid nitrogen trap to condense $^{30}PH_3$.

– Separation of ^{97}Ru formed via the ^{nat}Mo(^{3}He,xn)^{97}Ru process. The irradiated molybdenum was dissolved in a mixture of H_2SO_4, HNO_3 and $HClO_4$ by gentle heating. Thereafter CrO_3 solution in water was added and the oxidized RuO_4 was distilled over and collected in dilute HCl.

The distillation technique is apparently very useful for isolation of many elements. However, the purity of the product achieved may or may not be acceptable for medical application. A subsequent purification step may thus also be necessary.

Thermochromatography

Thermochromatography, like distillation, makes use of the volatility of compounds of elements. However, the various volatile species remain in the column with a temperature gradient and are deposited at different distances from the original location of the solid target. This gas phase separation method was developed and extensively used at the Joint Institute of Nuclear Research, Dubna, Russia, for investigations on super heavy elements and decay properties of some spallation products. Extensive work was carried out later at the Paul Scherrer Institute, Villigen, Switzerland, which was also related to super heavy elements. As far as the medical radionuclide production is concerned, the technique was first applied at the Forschungszentrum Jülich in the large-scale production of ^{75}Br and ^{77}Br (see Appendix II). A Cu_3As target, irradiated with 100 μA beam of 36 MeV ^{3}He-particles to produce ^{75}Br via the ^{75}As(^{3}He,3n)-reaction, was introduced in the thermochromatographic column placed in an oven at 950 °C (see Fig. 4 in Appendix II). Radiobromine separated from the target was carried over by a He stream and got condensed in the tube at a certain distance from the target. It was recovered by rinsing with 0.5 mL of water. Similarly, for the production of ^{77}Br via the ^{75}As(α,2n)^{77}Br reaction, the Cu_3As target was irradiated with 100 μA beam of 28 MeV α-particles and the thermochromatographic separation was performed. Both ^{75}Br and ^{77}Br were found to be in the form of bromide (>95%). The thermochromatographic apparatus was completely automated and controlled by a microcomputer. Another radionuclide produced and separated by the thermochromatographic method was ^{73}Se. Two nuclear processes used were ^{75}As(p,3n)^{73}Se on a Cu_3As target and ^{70}Ge(α,n)^{73}Se on a $Cu_3{}^{70}$Ge target. The separation of radioselenium from the Cu_3As target, irradiated with 40 MeV protons, was carried out utilizing an oxygen stream [133]. In the second case, a thin layer of electrodeposited $Cu_3{}^{70}$Ge alloy on a wedged Cu-backing was irradiated with 28 MeV α-particles at a beam current of about 100 μA and the radioselenium formed was separated by thermochromatography in a helium stream [134].

Besides the application of the horizontal thermochromatographic system, a vertical apparatus was also developed [135]. It is shown in Fig. 4.2. It consists of a wide quartz tube (Ø = 5 cm) in which two narrower quartz tubes (Ø = 2 and 3 cm) can be fitted in. The irradiated target material is introduced into the open wide tube and the apparatus is closed after inserting the narrower quartz tubes. The whole assembly is

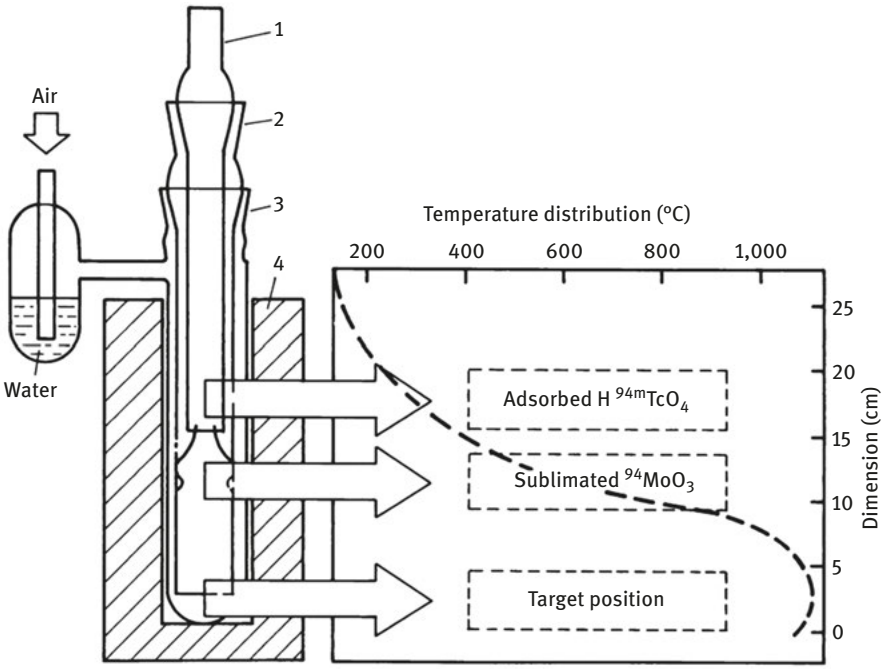

Fig. 4.2: Schematic representation of apparatus for thermochromatographic separation of ^{94m}Tc from irradiated $^{94}MoO_3$ target: 1, inner quartz tube for adsorption of ^{94m}Tc; 2, middle quartz tube for condensation of $^{94}MoO_3$; 3, outer quartz tube; 4, electric resistance oven. The zones of ^{94m}Tc adsorption and $^{94}MoO_3$ condensation are shown. Taken from Rösch et al [135], with courtesy of De Gruyter.

placed in a vertical oven with the required temperature distribution, and the reactant gas is passed through it. At the end of the separation process, the apparatus is taken out of the oven and cooled, and from it the inner narrow tube is removed with the adsorbed product. On rinsing the deposition spot of the product with a minimum volume of an appropriate solution, the desired radionuclide is obtained. This apparatus was first developed to separate ^{94m}Tc from a $^{94}MoO_3$ target irradiated with protons [135]. As flow gas moist oxygen was used. Subsequently the apparatus was also used to separate a few other systems. Recently it is being adapted to separate ^{99m}Tc produced via the $^{100}Mo(p,2n)$ reaction at a cyclotron.

It should be mentioned that thermochromatography was successfully utilized to separate several product radionuclides when the irradiation was done at a small or medium-sized cyclotron (Levels II–IV). The collected radioactive product, however, though radionuclidically pure, may not always exist only as one species. It may then be necessary to introduce a second purification step. This was done, for example, in the case of the separated ^{94m}Tc mentioned above. The activity collected in a small volume of 10^{-4} M NaOH solution contained some impurity besides Tc(VII). On

passing the solution through a small alumina column, the eluted technetium activity was found to be >99% $^{94}TcO_4^-$ (see Fig. 6 in Appendix V). It may also be emphasized that in case the target is irradiated with high-energy projectiles, the thermochromatographically separated product may not meet the purity demands. In that case, the thermochromatography may simply remove the radioactive product from the bulk target, that is, it would allow to concentrate the radionuclide in a small volume of the rinsing solution. A subsequent separation step could then enhance the purity of the radionuclide to the desired standard.

Solvent Extraction

Solvent extraction involves distribution of a solute between two immiscible phases, with enhanced concentration in one phase. The solutes are mostly metal ions and the two phases are aqueous and organic, although other types of liquid–liquid systems, for example, molten salts or liquid metals, may also occur. In most cases, a transfer of the metallic radionuclide to an organic phase is desired. There are many factors which affect this transfer. Some of them are as follows:

- concentrations of reagents and the extracted species,
- ratio of volumes of the two phases,
- temperature of the system and mixing time,
- pH value of the aqueous system.

Under optimised conditions, the technique can be applied to a large number of systems. It has been extensively used in radiochemistry. The method works over a very wide range of concentrations, from concentrated solutions in nuclear industry, involving uranium production or nuclear fuel reprocessing, to single atom separations in search of the heaviest elements. The processes related to medical radionuclide production involve concentrations somewhere in between.

In the aqueous phase, the radioactive metal radionuclide under consideration may be present as free metal ion or as positive, negative or neutral complex. Its extraction in an organic phase, however, can take place only as a neutral aggregate or chelate. For example, ^{52}Fe formed via the $^{52}Cr(^3He,3n)^{52}Fe$ reaction is extracted in ether as $^{52}FeCl_3$ after dissolution of the target in HCl. In general, however, the extraction of an inorganic species occurs only after its interaction with a chelating organic molecule. Very commonly the chelating agent is dissolved in a non-polar organic solvent. Some of the examples are theonyl trifluoro acetone dissolved in benzene, di-(2-ethylhexyl) phosphoric acid dissolved in *n*-heptane and so on. An organic reagent may form extractable complexes with several elements, but, under proper conditions, selective extraction of a single element is possible. The extraction process is then described in terms of the distribution ratio, given by

$$D = \frac{C_{org}}{C_{aq}}$$

where C_{org} is the total analytical concentration of the metal radionuclide in the organic phase and C_{aq} the analytical concentration in the aqueous phase. D is simply the ratio of the specific activities of the phases. The radionuclide concentrated in the organic phase has finally to be back extracted into an aqueous phase.

In medical radionuclide production, the solvent extraction technique is occasionally used either alone or in combination with some other preconcentration technique. Among the most common examples are the purification of ^{67}Ga and ^{111}In formed via the ^{68}Zn(p,2n)^{67}Ga and ^{112}Cd(p,2n)^{111}In reactions, respectively. Extraction of the two radionuclides is done in diisopropyl ether from HCl and HBr solution, respectively, and back extraction is easily achieved in a small volume of 0.05 M HCl. A more demanding case is the separation of radioselenium formed via the ^{75}As(p,xn)^{73,75}Se process. Attempts to separate it from an irradiated As_2O_3 target were not very successful. Using a Cu_3As target, however, radioselenium was first removed from the bulk material by thermochromatography [cf. 133], then dissolved in 6 M HCl and thereafter subjected to solvent extraction [133]. After reduction with SO_2, extraction was done with benzene. The apparatus used is shown in Fig. 4.3.

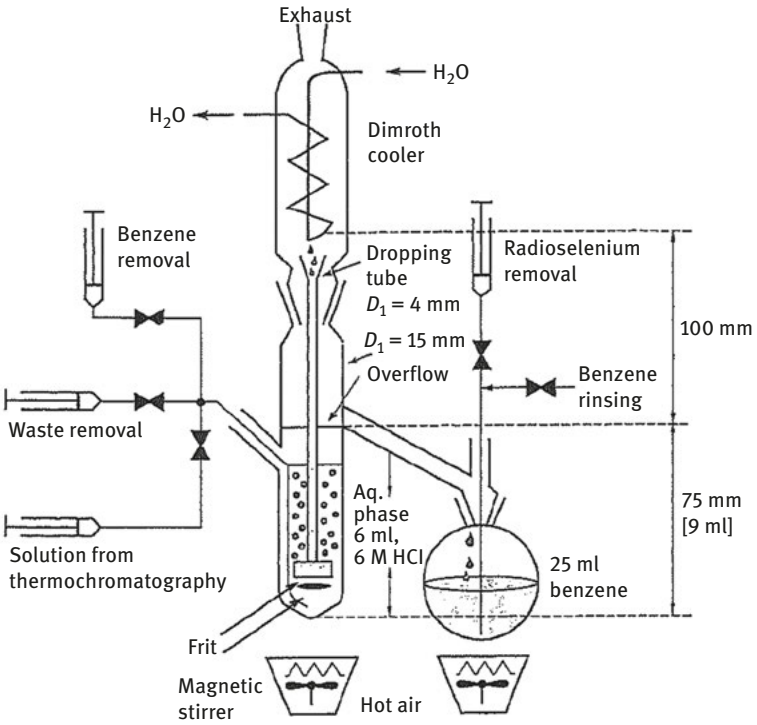

Fig. 4.3: Apparatus for extraction of radioselenium in benzene from a solution containing thermochromatographically separated radioselenium. Taken from Blessing et al. [133], with courtesy of De Gruyter.

It consists of a round bottom distillation flask connected to an extractor in the form of a perforator. Benzene is distilled; some of it condenses around the Dimroth cooler and falls through a funnel into the dropping tube having a frit at the end. With the magnetic stirrer on, the reduced radioselenium solution is injected into the extractor. By adjusting the benzene dropping rate at 5 mL min^{-1} under continuous stirring, the radioselenium is extracted quantitatively in the organic phase within about 35 min (cf. Fig. 4.4).Thereafter the aqueous phase is separated via the waste removal part and the radioselenium concentrated in benzene. The elemental radioselenium in benzene was found to be chemically very reactive. Some other solvent extraction systems specifically used to separate several medical radionuclides are mentioned in the next chapters.

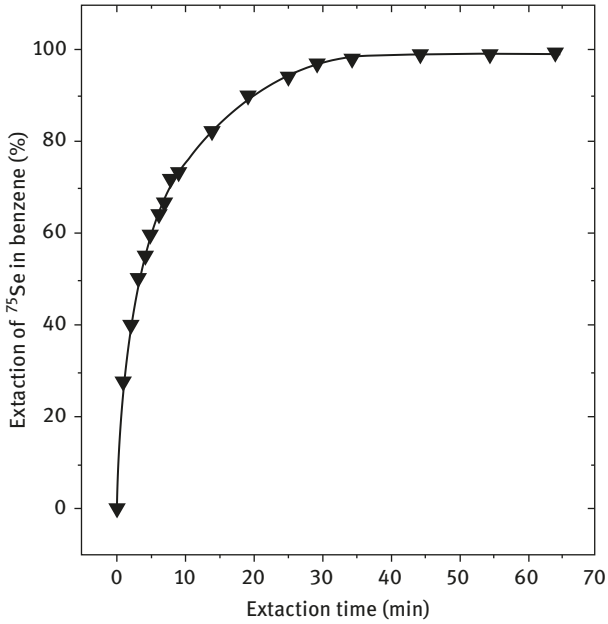

Fig. 4.4: Extraction yield of radioselenium in benzene as a function of time. Taken from Blessing et al. [133], with courtesy of De Gruyter.

Ion-Exchange Chromatography

Ion-exchange chromatography involves adsorption of ions on an ion exchanger, followed by selective elution of individual elements. Most common ion exchangers are synthetic organic polymers having a functional group (they are termed as *resins*). Both anion and cation exchangers are used in separation of metal radionuclides. An anion exchanger contains one of the three groups $-(CH_2NR_3)Cl$, $-(CH_2NHR_2)Cl$ or $-(CH_2NH_2R)Cl$, whereby R denotes an alkyl chain. A cation

exchanger typically consists of a sulfonic acid group attached to a cross-linked polystyrene matrix (i.e., $R–SO_3^-$). In this case, the exchange reaction can be written as

$$R–SO_3^- \ldots. H^+ + M^+X^- \leftrightarrow R–SO_3^- \ldots. M^+ + H^+X^-$$

where M^+ is a metal ion and X^- is an anionic ligand. For this reaction the equilibrium constant k_1 can be written as

$$k_1 = \frac{[R-SO_3^- \ldots.M^+]_a[H^+X^-]_b}{[R-SO_3^- \ldots.H^+]_a[M^+X^-]_b} \text{ (at equilibrium)}$$

where a is the concentration in resin and b the concentration in solution.

In a separation cycle the equilibrium constant for different metals are different. Thus in principle, a separation is always possible. However, due to very small differences in equilibrium constants, especially in the case of metals of similar chemical properties, for example, lanthanides, many cycles are needed. Nonetheless, it is possible to separate the lanthanides from one another using this technique, which otherwise are very difficult to separate.

The experimental procedure in applying this separation technique consists of loading a column of appropriate dimensions with an anion or cation exchanger, followed by its conditioning through flow of appropriate reagents. Thereafter the irradiated target dissolved in an appropriate solvent is transferred to the column, whereby the product radionuclide is generally adsorbed. On changing the eluent and maintaining well-defined conditions, it is possible to selectively elute the desired radionuclide from other products. Thus in principle, the technique is simple but considerable optimisation work is needed to obtain satisfactory results.

In general, the ion-exchange technique works very well when the amounts of the substances put on a column are small so that the column is not overloaded. In fundamental studies on nuclear reactions a thin irradiated sample weighing a few milligrams may be dissolved in a solvent and transferred to a small resin column, and the reaction products could be sequentially eluted for radioactivity measurement. In a real radionuclide production run at a low to medium-sized cyclotron, however, 0.2–0.5 g of the target is generally used; at intermediate energies even a thicker target may be used. Dissolving and transferring such a target to an ion-exchange column causes a heavy load. Since the target element and the product elements have generally adjacent Z values, the separation peaks may not be well resolved. In production processes, therefore, one of the two strategies is followed:

a) A system is chosen in which the bulk target element runs through, but the product elements in tracer quantities are adsorbed on the column. They are then eluted using another eluent. The system is used in a modified form if both the bulk target and the reaction products are adsorbed on the column. Conditions are then chosen such that the desired radionuclide is eluted first.

b) The product radionuclide is separated from the target through coprecipitation with a small amount of a non-isotopic carrier, followed by an ion-exchange separation of the radionuclide from the non-isotopic carrier.

As an example of the first strategy, the results on the separation of radioiodine from an antimony target irradiated with α-particles are discussed [136, 137]. In one system [136], about 200 mg of 99.45% enriched ^{121}Sb in the form of a pressed pellet was irradiated with 26 MeV α-particles. The radionuclide ^{124}I was formed via the ^{121}Sb(α,n)^{124}I reaction. After the irradiation, the pellet was dissolved in hot 10 mL of 7 M HCl with a few drops of H_2O_2 and the solution was transferred to a pretreated Amberlyst A21 anion-exchange column (Ø = 1 cm, length = 30 cm). Antimony was eluted with 100 mL of 7 M HCl. The fraction was collected for recovery of the enriched material. The radioiodine was then eluted with 20 mL of 5 mM tetrabutyl ammonium bromide solution in ethylacetate (with a few drops of sodium dithionate) and the fraction was collected. Finally the column was washed with 35 mL of 2 M HCl to remove radiotellurium. In another system [137], about 200 mg of $^{nat}Sb_2O_3$ in the form of a pellet was irradiated with 38 MeV α-particles, whereby ^{124}I was formed via the ^{123}Sb(α,3n)^{124}I reaction. The irradiated pellet was dissolved in 30 mL of 7 M HCl and then transferred to an anion-exchange column (Amberlyst A26, Ø = 1 cm, length = 20 cm). Successive elutions with tetrabutyl ammonium hydrogen sulfate, 2 M HCl and 0.7 M NaOH led to a complete separation of ^{124}I from ^{121}Te and bulk of Sb. The elution curves are shown in Fig. 4.5

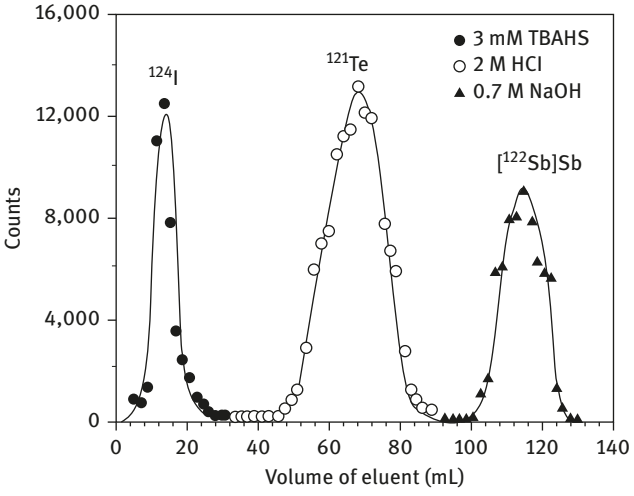

Fig. 4.5: Elution profile of radioiodine, radiotellurium and carrier-added ^{122}Sb from the anion-exchange column Amberlyst A26 using various eluents, taken from Uddin et al. [137], with courtesy of De Gruyter.

[137]. The volume of the collected ^{124}I fraction in both the separation schemes [136, 137] was somewhat large, but due to the relatively long half-life of ^{124}I, the activity could be concentrated in a smaller volume of the solution.

A good example of the second strategy, that is, removal of the radionuclide by coprecipitation, is furnished by the separation procedure used in the production of ^{86}Y via the ^{86}Sr(p,n)^{86}Y reaction. A 97% enriched $^{86}SrCO_3$ pellet weighing about 200 mg was irradiated with 17 MeV protons. Thereafter it was dissolved in a small volume of concentrated HCl, and 2 mg La was added as carrier. On addition of NH_4OH solution, lanthanum was precipitated as $La(OH)_3$, carrying ^{86}Y (in tracer quantity) with it. After centrifugation, the $La(OH)_3$ precipitate was taken up in a few drops of HCl and the solution was transferred to a small column (Ø = 4 mm, length = 40 mm) filled with Aminex A5 cation exchanger, whereby both ^{86}Y and La were adsorbed. Elution of the column was then done with α-hydroxyisobutyric acid (α-HIB). The ^{86}Y activity was eluted first and the whole activity could be collected in 150 µL of solution [138] (see Fig. 5 in Appendix V). Originally the separation was done at normal pressure, but later it was adapted to a high-performance liquid chromatography system [139].

In general, ion-exchange chromatography, also termed now as *ion chromatography*, is commonly used in the separation of radionuclides produced for medical application, provided the bulk effect of the target material is overcome by a pre-separation step. Thus, separations of the radionuclides ^{52}Mn, ^{52}Fe, ^{64}Cu, ^{67}Ga and ^{89}Zr have been achieved through the ion-chromatographic technique. In recent years, new types of resins are being synthesized and their use in analytical radiochemistry is increasing. Furthermore, some nanomaterials are being developed for use in radiochemical separations. Both those approaches have great potential for specific separations of several novel radionuclides presently under development for medical applications.

Electrolytic Separation

The electrolytic method of separation involves the removal of the desired product using an electric potential. However, the procedure is often slow and not very specific. It is used more in preparation of thin uniform samples for irradiations for nuclear data measurements (as discussed in Chapter 2) or for preparing thicker samples for large-scale production of a radionuclide using an inclined target (as described in Chapter 3) rather than in separation of reaction products. Nonetheless, it has been applied successfully or appears to be potentially useful in separation of several medical radionuclides from the bulk media. Three prominent cases are ^{18}F, ^{55}Co and ^{86}Y. They are discussed below.

For the electrochemical separation of ^{18}F formed through the ^{18}O(p,n)^{18}F reaction in a $H_2{}^{18}O$ target, a special cell was developed [140], which is shown in Fig. 4.6.

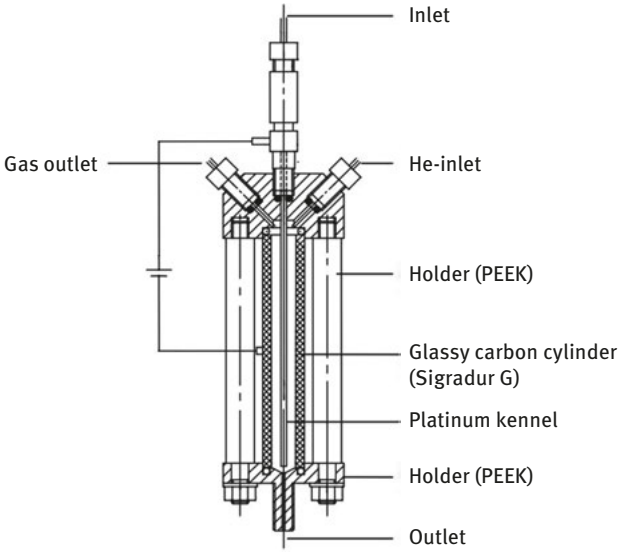

Fig. 4.6: Cell design for electrochemical separation of no-carrier-added $^{18}F^-$ from proton irradiated $H_2{}^{18}O$ for subsequent ^{18}F-fluorination reactions. Taken from Hamacher et al. [140], with permission from Elsevier.

It consists of a heatable cylindrical glassy carbon vessel that serves as the anode. A centric platinum kennel serves as the cathode and is also used to fill or empty the cell. The distance between the two electrodes is 2.7 mm. The irradiated water (1.3 mL) was transferred to the electrochemical cell and an electric field of about 50 V cm^{-1} was applied for 5 min, whereby > 96% of the ^{18}F activity was deposited on the carbon cylinder. The defluorinated target water was transported out of the cell using a gentle stream of helium. Thereafter, the electric field was changed to opposite polarity and a solution of the phase transfer catalyst in a dipolar aprotic solvent, for example, dimethylformamide was filled into the electrochemical cell. On applying a current of about 10 V cm^{-1} at a temperature of 100 °C, about 90% of the ^{18}F activity was desorbed from the carbon walls and went into the solution, which was then used for synthesis of radiopharmaceuticals.

Another cell was developed [109] in connection with the production of ^{55}Co via the $^{58}Ni(p,\alpha)^{55}Co$ reaction. It was used for electroplating and later for deplating. The cell was made of quartz glass in which a wedged target head made of Cu could be introduced. This acted as the cathode. A rotating platinum wire served as the anode. The cell was filled with the electrolytic solution consisting of ^{58}Ni dissolved in weak HCl and boric acid. On applying a current of 50 mA, ^{58}Ni was deposited on the cathode (wedged target). This target was then irradiated with 18 MeV protons. Thereafter, it was retransferred to the same electrolytic cell as used for electroplating. About

5 mL of 8 M HCl was then filled in the cell, the electrolytic circuit closed and the polarity was reversed. The radionuclide ^{55}Co and the inactive target nuclide ^{58}Ni went into solution and were thus separated from the Cu backing. Further processing of the solution was then done using anion-exchange chromatography, whereby ^{55}Co was obtained in a pure form.

With regard to the electrochemical separation of ^{86}Y formed via the ^{86}Sr(p,n)^{86}Y reaction, the irradiated target was dissolved in dilute HNO_3 in a beaker, two Pt plates were plunged for use as electrodes and were fixed 3 mm apart [141]. The electrolytic deposition was performed at a constant current of 450 mA at 50 °C. The radionuclide ^{86}Y was deposited on the cathode, which was removed from the electrolytic cell, washed with acetone and then transferred to another beaker filled with dilute HNO_3, in which a Pt wire was also inserted. By changing the polarity, the Pt plate became the anode and the Pt wire the cathode. During the electrolytic procedure the ^{86}Y was removed from the Pt plate and got deposited on the Pt wire. Finally, ^{86}Y was dissolved from this wire in 300 μL of dilute HCl.

4.2.3 Other Separation Methods

Besides the above mentioned separation methods commonly or occasionally used in clinical- or large-scale medical radionuclide production, in principle, use could also be made of a few other methods, for example, coprecipitation/scavenging/precipitation, electrophoresis, collection of recoiling products, extraction chromatography, mass separation and so on. The coprecipitation and scavenging are used to concentrate the desired radionuclide in a precipitate of a non-isotopic homologue (e.g., radioiodide on AgCl, radioyttrium on $La(OH)_3$) or on a precipitate of large surface area (e.g., radiolead on $Fe(OH)_3$). A subsequent separation of the radionuclide from the carrying element is essential. The technique of precipitation is occasionally applied to remove the bulk of the target material, but the desired radionuclide should remain in the solution so that it can be recovered by another step (e.g., removal of strontium target material as $SrSO_4$ precipitate, whereby the desired radioyttrium formed via the (p,n) reaction remains in solution). The electrophoresis involves movement of a chemical species in the liquid phase from another species under the influence of an electric field. However, to date this technique has not been used in medical radionuclide production.

The technique of recoil collection has been extensively applied in the separation of short-lived nuclear reaction products from irradiated targets using the *gas jet* method, which involves the formation of aerosols that can be carried to relatively long distances. However, those studies are all for fundamental investigations and not for separation of medical radionuclides. Regarding the medical radionuclides, the Szilard–Chalmer's process is of more interest (cf. Chapter 1), in which the recoiling product formed as a consequence of a nuclear transformation (nuclear

reaction or radioactive decay) may be in a chemical form different from that of the parent: it can then be separated. Small amounts of ^{51}Cr with enhanced specific activity have been obtained following the ^{50}Cr(n,γ)^{51}Cr process.

The extraction chromatography consists of a combination of solvent extraction and column chromatography. It involves loading a carrier column with a complex-forming reagent, sucking the solution of the irradiated material through the column, whereby the radioactive species forms a complex and is adsorbed, followed by selective elution of the complex using a suitable eluent. An example is the separation of lanthanides: Di(2-ethylhexyl)orthophosphoric acid is adsorbed on a silicagel column and the irradiated lanthanide dissolved in HNO_3 is transferred onto it. Elution of lanthanides is then done with 6 M HNO_3, whereby the sequence of elution of lanthanide is from lightest to the heaviest (opposite to that in cation-exchange chromatography). This technique has been partly used in medical radionuclide production.

In contrast to the above mentioned radiochemical separation techniques, a more physical method, namely, mass separation, has also been extensively utilized in studies on short-lived radionuclides rather far from the stability line of elements. It is based on the charge/mass ratio of each product radionuclide. Mass separators have been constructed to separate, on one hand fission products and, on the other, spallation products. Like the *gas jet* method (see above), the use of mass separators has also been related more to fundamental investigations. In recent years, however, great progress has been made at CERN in Geneva through the development of an online mass separator, and a large number of radionuclides generated via the spallation process could possibly be made available in quantities sufficient for tracer or even preclinical studies. Two potentially interesting radionuclides produced this way [cf. 99, 142] are the α-emitter ^{149}Tb ($T_{1/2}$ = 4.1 h) and the β^+ emitter ^{152}Tb ($T_{1/2}$ = 17.5 h).

Competing Separation Methodologies

If a radionuclide is demonstrated to be clinically interesting, then more efforts are devoted to the development of versatile chemical separation methods, and several competing separation methodologies may be elaborated and practically applied. For example, the radionuclide ^{131}I is separated by both dry and wet distillation techniques, the radionuclide ^{67}Ga by ion-exchange and solvent extraction techniques and the radionuclide ^{86}Y by ion-exchange and electrolytic methods. The method of choice then depends on the interest and capability of a particular laboratory.

It should also be pointed out here, that although in production of many radionuclides at low-energy cyclotrons a simple one-step separation procedure may be sufficient, in production of many radionuclides involving intermediate energy reactions, spallation or fission process, a combination of several techniques is necessary to obtain the desired radionuclide in a pure form. Those combinations of techniques specific to some very important standard and novel

radionuclides are discussed in Chapters 5 and 6, respectively, along with other aspects of production processes.

4.3 Quality Assurance of the Separated Radionuclide

The last important step in a chain of operations for the production of a radionuclide consists of quality assurance of the finally separated product. In general, four characteristics need to be observed. These are radionuclidic purity, radiochemical purity, chemical purity and specific activity. A brief discussion of each item is given below (see also Appendix V).

The *radionuclidic purity* means the absence of other radionuclides. This is achieved via the choice of a suitable nuclear process and energy range, combined with a clean chemical separation. The radionuclide ^{124}I, for example, is produced today mainly using the ^{124}Te(p,n)-reaction on a highly enriched $^{124}TeO_2$ target over the energy range of $E_p = 12 \rightarrow 8$ MeV, because the resulting product is very pure (^{125}I impurity < 0.1%). The radionuclidic purity is generally tested by high-resolution γ-ray spectrometry.

The *radiochemical purity* means that the radiochemically separated product is in the form of one major chemical species. It is generally achieved and tested by radiochromatographic methods, such as thin layer chromatography, high-performance liquid chromatography and so on.

The *chemical purity* means the absence of inactive impurities that are generally introduced via the chemical reagents used in the production of the radionuclide. The chemical purity appears to be more important in the case of metal radionuclides than for radionuclides of organic elements. This is due to high sensitivity of metal–chelate bond formation on foreign ions than in the labelling of organic compounds with radionuclides. For checking the chemical purity of a radioactive product, one or more of the standard techniques, such as atomic absorption spectroscopy, ultraviolet (UV) or infrared (IR) detection, inductively coupled plasma-mass spectrometry (ICP-MS) and polarography, are used.

The *specific activity* is defined as the radioactivity per unit mass of the product (see Chapter 1). Cyclotron production of radionuclides leads generally to high specific activity products, unless some carrier inadvertently gets introduced by impure target material during the chemical processing stage. For estimating the specific activity, generally the radioactivity of the whole batch is measured in an ionization chamber and the mass is determined using a sensitive detection method, such as UV, IR, refractive index or conductivity measurement.

It should be pointed out that the above discussed four quality assurance tests refer to the radionuclide in its original form. They are crucial with respect to further processing of the product. If the radionuclide is to be converted into a radiopharmaceutical for human use, several further stringent tests, like those for sterility, apyrogenicity and toxicity, also become mandatory.

4.4 Use of Highly Enriched Isotopes as Target Materials and their Recovery

Many of the standard medical radionuclides are produced using materials of natural isotopic composition. However, in some cases the necessity exists to use isotopically enriched isotopes as targets because of one of the following two reasons:

i) greater demand on yield, purity or specific activity of the desired product,
ii) non-availability of a cyclotron with suitable particles and energy for a particular production reaction.

In recent years, highly enriched isotopes have been finding increasing application in medical radionuclide production, especially at cyclotrons. Three typical examples are as follows:

a) Production of the SPECT radionuclide ^{123}I ($T_{½}$ = 13.2 h) via the ^{124}Xe(p,2n)^{123}Cs → ^{123}Xe → ^{123}I process using 99.8% enriched ^{124}Xe gas as target material.
b) Production of the standard PET radionuclide ^{18}F ($T_{½}$ = 109.8 min) via the ^{18}O(p,n)^{18}F reaction using 98% enriched $H_2{}^{18}O$ as target material.
c) Production of the non-standard PET radionuclide ^{64}Cu ($T_{½}$ = 12.7 h) via the ^{64}Ni(p,n)^{64}Cu reaction using >95% enriched ^{64}Ni electroplated on a Au backing as target material.

The natural abundances of the above mentioned three target isotopes are low, namely, ^{124}Xe (0.0952%), ^{18}O (0.205%) and ^{64}Ni (0.9256%). Bringing those isotopes to high enrichment for use as target materials in medical radionuclide production is thus an expensive enterprise. It is therefore mandatory to develop high-class irradiation technology that would avoid the loss of the material during irradiation. In the three examples given above, related to the production of ^{123}I, ^{18}F and ^{64}Cu, sophisticated gas, liquid and solid targetry, respectively, are involved. Furthermore, efficient chemical procedures have been devised to isolate the desired radionuclides and to recover the enriched targets for reuse. Detailed information on the various enriched isotopes used as targets is given in the next two chapters.

4.5 Concluding Remarks

In this chapter some general considerations with regard to chemical processing of irradiated materials have been enumerated. The principles of various dry and wet chemical separation procedures used at the no-carrier-added level have been outlined and a few pertinent examples are presented. For a certain radionuclide formed, generally several separation methods may be applicable. The choice of a particular process for routine production, however, depends on the defined criteria of yield and purity of the desired radionuclide. The separated product must

meet the quality requirements with respect to radionuclidic, radiochemical and chemical purity, as well as specific activity. Finally, the highly enriched target material, if used in the production process, must be efficiently recovered for reuse.

It is, however, pointed out that the description and application of the radiochemical separation techniques mentioned in this chapter should serve only as typical examples. Some more detailed descriptions of production technologies of the standard medical radionuclides are given in Chapter 5 and those of novel radionuclides in Chapter 6. Furthermore, Appendices II, III, V and VI provide some supplementary information on various production processes.

5 Production of Standard Medical Radionuclides

As mentioned in earlier chapters, the production of radionuclides is carried out using nuclear reactors as well as accelerators/cyclotrons. Some of the fundamental nuclear, radiochemical and irradiation aspects have been considered in Chapters 1–4. In the following two chapters, the production technology is treated in somewhat more detail. This chapter describes the routine production of standard radionuclides for state-of-the-art patient care studies and Chapter 6 the development of novel radionuclides.

The standard medical radionuclides, that is, those routinely used in diagnosis, therapy or biomedical studies (see Chapter 1) are listed in Table 1.1 together with their decay data under four headings, namely soft radiation emitters (i.e., soft β^- emitters for in vitro studies or X-ray and Auger electron emitters for internal therapy), γ-ray emitters for SPECT, positron emitters for PET and β^- and α-particle emitters for internal therapeutic applications. Those groups are treated individually later.

The production methods of some of the radionuclides are very well established (cf. [25, 26, 41, 53, 143, 144] and Appendices II, III and VI), while in many other cases good knowledge is available. In this chapter, therefore, only some salient points are described. For a few radionuclides, some newer information has been reported in recent years. Those aspects are treated in somewhat more detail.

5.1 Standard Soft Radiation Emitters

The common methods of production of soft radiation emitters are listed in Table 5.1. Besides nuclear data, the target materials used and typical batch yields achieved are also given. They are all produced in large amounts using a nuclear reactor, except for ^{103}Pd which is now produced using a cyclotron. The very low-energy β^--emitting radionuclides ^{3}H and ^{14}C have contributed tremendously to biochemistry and pharmacology in enhancing our understanding of kinetic, metabolic and physiological behaviours of biomolecules and research substances. This was due to very low radiation hazard caused by them. Although only in vitro studies could be performed, the universal availability of those radionuclides as well as their relative ease of detection by liquid scintillation counting (LSC) made them very popular tracers in drug development research. The radionuclide ^{125}I with its low-energy radiation emissions is very well suited for autoradiography and is commonly used in radioimmunoassay or receptor binding studies. It is also used in brachytherapy as implant seeds (utilizing X-rays) and in cell-targeted therapy (utilizing the shower of Auger electrons created in its decay). Over the last 20 years ^{125}I has been partly replaced by ^{103}Pd as far as brachy-

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Table 5.1: Common methods of production of standard soft radiation emitters.

Radionuclide	$T_{½}$	Production route	Cross section[a] (barn)	Target material	Typical experimental batch yield (GBq)
^{3}H	12.3 a	$^{6}Li(n,\alpha)$	940	Li, LiF	>500
^{14}C	5730 a	$^{14}N(n,p)$	1.81	AlN	20
^{33}P	25.3 d	$^{33}S(n,p)$	1.6×10^{-3}	^{33}S [b]	75
		$^{36}Cl(n,\alpha)$	0.59×10^{-3}	$K^{36}Cl$ [b]	75
^{35}S	87.5 d	$^{35}Cl(n,p)$	0.49	KCl	370
^{125}I	59.4 d	$^{124}Xe(n,\gamma)^{125}Xe$	$\sigma_{th} = 114$	^{nat}Xe	30
		$^{125}Xe \xrightarrow{EC} {}^{125}I$	$I_o = 3191$ [c]	^{124}Xe [b]	120
			FS = 0.44		
^{103}Pd	17.0 d	$^{103}Rh(p,n)$ $E_p = 13 \rightarrow 7$ MeV	6.5 MBq μA h^{-1} [d]	Rh metal	50

[a] Averaged for fission neutron spectrum, unless otherwise stated, values are taken from [42].
[b] Isotopically enriched.
[c] Cross section for thermal neutron capture (σ_{th}), resonance integral (I_o) and averaged for fission neutron spectrum (FS). These are recently evaluated values [41].
[d] Yield calculated from the excitation function for the given energy range for 1h irradiation [93].

therapy is concerned, because the X-ray energies in both cases are similar but the half-life of ^{103}Pd is much shorter. The radionuclides ^{33}P and ^{35}S have not found the same wide application as the other four radionuclides; they are, however, often used in metabolic turnover studies. In those two cases also the determination of radioactivity is carried out via LSC.

^{3}H ($T_{½}$ = 12.3 a), ^{14}C ($T_{½}$ = 5730 a); ^{33}P ($T_{½}$ = 25.3 d) and ^{35}S ($T_{½}$ = 87.5 d)

Tritium is produced by irradiation of Li or Li-containing compounds with neutrons in a nuclear reactor. The reaction cross section is very high and charges in excess of 500 GBq are commonly produced. Tritium is isolated as $^{3}H_2$ gas or as $^{3}H_2O$ (tritiated water). For the production of ^{14}C, generally a metal nitride is irradiated. The cross section of the (n,p) reaction used for production is fairly high but due to relatively long half-life of ^{14}C, its batch yield amounts to about 20 GBq. The radionuclide is separated as $^{14}CO_2$ or as $Ba^{14}CO_3$. For the production of ^{33}P, a 60–68% enriched ^{33}S target in elemental form or a $K^{36}Cl$ target is irradiated with reactor neutrons. The method was developed at the Oak Ridge National Laboratory [26]. The batch yields of ^{33}P from the two processes were similar due to higher neutron flux used in the latter case. The desired product is separated by solvent extraction, whereby the enriched target material is also recovered. The product is finally available as $H_3{}^{33}PO_4$. With regard to the production of *^{35}S*, a KCl target is irradiated in a nuclear reactor

for several months and the chemical separation of the desired product is carried out via ion-exchange chromatography [26]. The radionuclide is then generally available as $H_2{}^{35}SO_4$ in batch yields of about 370 GBq. It should be noted that for the latter two radionuclides, namely ^{33}P and ^{35}S, the cross sections of the (n,p) reactions involved are in the mb range, and are thus much smaller than that for the production of ^{14}C, yet due to the much shorter half-lives of ^{33}P and ^{35}S as compared to that of ^{14}C, they are obtained in good batch yields.

^{125}I ($T_{½}$ = 59.4 d)

The radionuclide ^{125}I is produced via the nuclear process $^{124}Xe(n,\gamma)^{125}Xe \xrightarrow[16.9h]{EC} {}^{125}I$. For this purpose generally an Al capsule, filled with natural xenon (or occasionally with enriched ^{124}Xe) up to a pressure of about 5 bar, is irradiated in a nuclear reactor for about 100 h. The capsule is then taken out of the reactor and a waiting time of about 100 h is allowed to let ^{125}Xe decay to ^{125}I. Thereafter, xenon is cryogenically removed from the capsule and the radioiodine deposited on the inner wall of the capsule is isolated by rinsing it with a small volume of 0.01 M NaOH solution. The final product is available as iodide. Large amounts of this radionuclide are produced at the Institute of Isotopes in Budapest. Occasionally, XeF_2 is also used as a target material because its melting point is fairly high (130 °C). The irradiated material is dissolved in water and the emanating Xe gas is collected in a cold trap. After a few days of decay, ^{125}Xe is cryogenically transferred to another cold trap and ^{125}I formed via the ^{125}Xe decay in the first cold trap is dissolved in a dilute solution of a mixture of NaOH and Na_2SO_3. It is claimed that the radioiodine exists in the form of iodide.

There are two important considerations with respect to the production of ^{125}I (i) Development of high-pressure capsules for reactor irradiations. A few laboratories are attempting to use carborundum capsules filled with Xe up to 100 bar. (ii) Limited duration of irradiation. In principle, a xenon capsule could be irradiated for several weeks to allow maximum production of ^{125}I because the half-lives of the parent ^{125}Xe and the daughter ^{125}I are very suitable. However, ^{125}I has a very high cross section for the $^{125}I(n,\gamma)^{126}I$ reaction (σ_{th} = 892 b; I_0 = 9300 b). Therefore, in long irradiations considerable amount of ^{126}I ($T_{½}$ = 12.93 d), a hard β^- and γ-ray emitter, will be accumulated as impurity. This will jeopardize the use of ^{125}I. A general recommendation is that the level of the ^{126}I impurity in ^{125}I should be <5%. This can be achieved only through a controlled short irradiation and post irradiation decay of ^{125}Xe in the capsule outside the neutron field, as mentioned above. The production batch yield is enough for wide distribution. Another recommendation is to use enriched ^{124}Xe as target material. In a few laboratories, this has been done and batch yields of about 120 GBq were obtained in 24 h irradiations.

^{103}Pd ($T_{½}$ = 17.0 d)

The radionuclide ^{103}Pd was originally produced via the ^{102}Pd(n,γ)^{103}Pd reaction in a nuclear reactor [26]. However, since the target isotope in natural Pd is only 1.02%, the specific activity of the product ^{103}Pd was very low. The problem was not alleviated even by using an enriched ^{102}Pd target. Due to the increasing demand for ^{103}Pd of high specific activity for application in prostate cancer therapy, for several nuclear processes were investigated (for review cf. [93]), and the ^{103}Rh(p,n)^{103}Pd reaction (see Fig. 2.17) is now routinely used. The calculated thick target yield is given in Fig. 5.1. As the target material Rh is rather expensive, a good separation of ^{103}Pd and recovery of Rh are mandatory. The Rh metal target (plated layer, foil or wire) irradiated with protons of suitable energy is frequently dissolved by sodium bisulfate fusion, or by static AC electrodissolution in hydrochloric acid [144]. Separation of ^{103}Pd from the solubilized Rh matrix is effected by several methods based on solvent extraction, anion or cation exchange chromatography. The target Rh is recovered by electrolysis. The final product used for seed preparation should preferably be no-carrier-added (nca) palladium chloride solution in dilute ammonium hydroxide. The accepted radionuclidic purity is at least 99.95% ^{103}Pd. On the other hand, in many cases, ^{103}Pd is not separated. The irradiated Rh in the

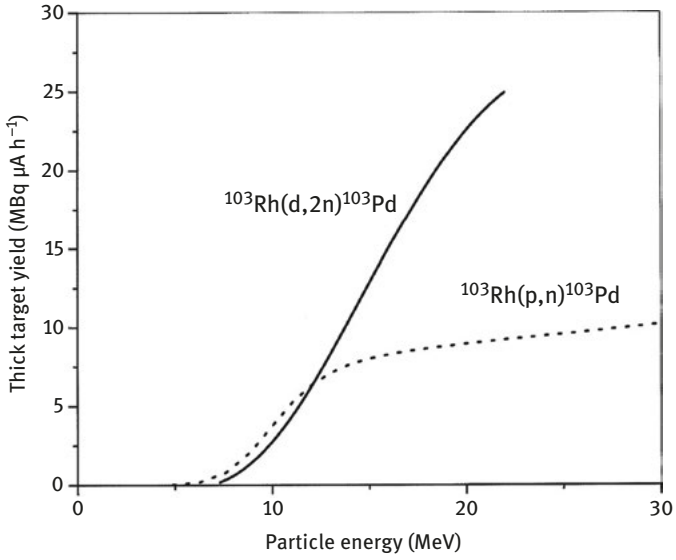

Fig. 5.1: Calculated integral yields of ^{103}Pd via the ^{103}Rh(p,n)^{103}Pd and ^{103}Rh(d,2n)^{103}Pd reactions as a function of projectile energy. Taken from Hussain et al. [93], with permission from Elsevier.

form of very thin seeds is introduced into the prostate, and the therapy effect is achieved through the X-rays coming out of the seed. In this case, however, it is mandatory that the proton energy does not exceed 13 MeV, so that the reaction ^{103}Rh(p,pn)^{102}Rh is not induced and the long-lived impurity ^{102}Rh ($T_{1/2}$ = 207 d) is avoided [143]. Using slanting beam targets and high current irradiations, batch yields of ^{103}Pd amounting up to 50 GBq have been achieved.

The great success in the application of ^{103}Pd in prostate cancer therapy led to the construction of about 20 medium-sized cyclotrons in the USA to produce exclusively this radionuclide. Furthermore, due to the much higher yield of the product achieved via the ^{103}Rh(d,2n)^{103}Pd reaction (cf. Fig. 5.1), attempts have also been made to use the deuteron beam. However, since the intensity of the deuteron beam is generally not as high as that of the proton beam, the method of choice for production of ^{103}Pd is still the ^{103}Rh(p,n) reaction. On the other hand, it should also be pointed out that because of a new competition between ^{103}Pd and ^{177}Lu, the use of ^{103}Pd has started declining.

5.2 Standard γ-Ray Emitters for SPECT

The production data of the five commonly used γ-ray emitters in diagnostic studies via SPECT are listed in Table 5.2. The yields of the radionuclides produced via charged-particle induced reactions were calculated from the evaluated excitation functions given in ref. [53].

The radionuclide ^{99m}Tc is by far the most commonly used SPECT radionuclide. It ideally emits a 140.5 keV photon and causes the least radiation dose to the patient. It is almost always available in a clinic via the ^{99}Mo/^{99m}Tc generator system. Furthermore, by virtue of its versatile complex formation chemistry, labelling methods have been established to rather easily bind technetium to various compounds. Also the radionuclide ^{123}I is commonly used. In fact, chemically seen, ^{123}I is superior to ^{99m}Tc. However, due to its lesser availability and higher cost, ^{123}I is much less broadly used than ^{99m}Tc. The third radionuclide, viz. ^{201}Tl, is extensively used for myocardial perfusion measurements. The remaining two radionuclides, namely ^{67}Ga and ^{111}In, form stable metal complexes and are therefore of great potential interest. However, their present use as SPECT agents is limited. They are now partly considered for therapeutic application because they emit a large number of Auger electrons. In the following, therefore, the production methods for ^{99m}Tc, ^{123}I and ^{201}Tl are discussed in more detail but only brief information is provided on ^{67}Ga and ^{111}In. Furthermore, ^{99m}Tc is generated using a reactor, whereas the other four radionuclides are produced at a cyclotron.

Table 5.2: Common methods of production of standard γ-ray emitters for SPECT.

Radionuclide	$T_{1/2}$	Production route	Energy range (MeV)	Calculated yield (MBq μA h^{-1})	Target material	Typical experimental batch yield (GBq)
^{67}Ga	3.26 d	^{68}Zn(p,2n)	25 → 18	180	^{68}Zn [a] (electroplated or pellet)	50
^{99}Mo (generator) ↓	2.75 d	^{235}U(n,f)	Reactor	FY = 6.13% [b]	$^{235}UAl_3$ [a]	>10^4
		^{98}Mo(n,γ)	Reactor	σ_{th} = 0.13 b; I_o = 6.9 b; FS = 14 mb [c]	MoO_3	150
^{99m}Tc	6.0 h				Al_2O_3 column (loaded with ^{99}Mo)	>5 (per generator)
^{111}In	2.81 d	^{112}Cd(p,2n)	25 → 18	166	^{112}Cd [a] (electroplated or pellet)	50
^{123}I	13.2 h	^{123}Te(p,n)	14 → 10	130	$^{123}TeO_2$ [a]	20
		^{124}Xe(p,x)^{123}Xe [d]	29 → 23	414 [e]	^{124}Xe gas [a]	70
		^{127}I(p,5n)^{123}Xe [d]	65 → 45	777 [e]	NaI	70
^{201}Tl	3.06 d	^{203}Tl(p,3n)^{201}Pb [f]	28 → 20	18 [g]	^{203}Tl [a] or ^{nat}Tl (electroplated)	50

[a] Isotopically enriched.
[b] Fission yield (see Chapter 2).
[c] Cross sections for thermal neutron capture, resonance integral and averaged for fission neutron spectrum, respectively, values are taken from Ref. [38].
[d] ^{123}Xe ($T_{1/2}$ = 2.1 h) decays 87% through EC and 13% via β^+ emission to ^{123}I.
[e] This is ^{123}I yield after 7 h decay of ^{123}Xe.
[f] ^{201}Pb ($T_{1/2}$ = 9.4 h) decays 100% via EC to ^{201}Tl.
[g] This is ^{201}Tl yield after optimum ^{201}Pb decay time of 32 h.

^{99m}Tc ($T_{1/2}$ = 6.0 h)

As mentioned earlier, ^{99m}Tc is available via the ^{99}Mo/^{99m}Tc generator. An Al_2O_3 column is loaded with ^{99}Mo and the daughter activity is periodically removed by elution with saline. The parent nuclide ^{99}Mo is produced at a nuclear reactor, and two routes are possible: ^{98}Mo(n,γ)^{99}Mo and ^{235}U(n,f)^{99}Mo. The cross section of the (n,γ) reaction is relatively small (see Chapter 2) and due to the use of ^{nat}Mo (with ^{98}Mo content of 24.13%) as target material, the specific activity of the ^{99}Mo produced is low. Thus, because of the heavy loading of the Al_2O_3 generator column with stable molybdenum, in spite of the rather big dimensions of the column, the risk of breakthrough of Mo is high and ^{99m}Tc eluate volumes are large. Somewhat higher specific activity is achieved using a high-flux nuclear reactor. However, such reactors are seldom available for radionuclide production. Furthermore, some gel and distillation generators have been developed but their overall efficiencies are not comparable to that of the

alumina column generator (see Appendix VI). The method of choice for production of ^{99}Mo for medical use is thus the fission process. The cross section for thermal neutron induced fission of ^{235}U is 596 barn and the cumulative yield of ^{99}Mo is 6.13% (see Chapter 2); thus large amounts of ^{99}Mo can be produced. However, the process puts a very heavy demand on the separation of nca ^{99}Mo from irradiated ^{235}U and other fission products. Furthermore, the highly enriched ^{235}U (HEU) target material has also to be recovered for reuse. A typical separation scheme is given in Fig. 5.2. Since the fission of ^{235}U is also associated with the formation of some α-emitting actinides, the purity requirements for ^{99}Mo are very stringent. Nonetheless, highly developed

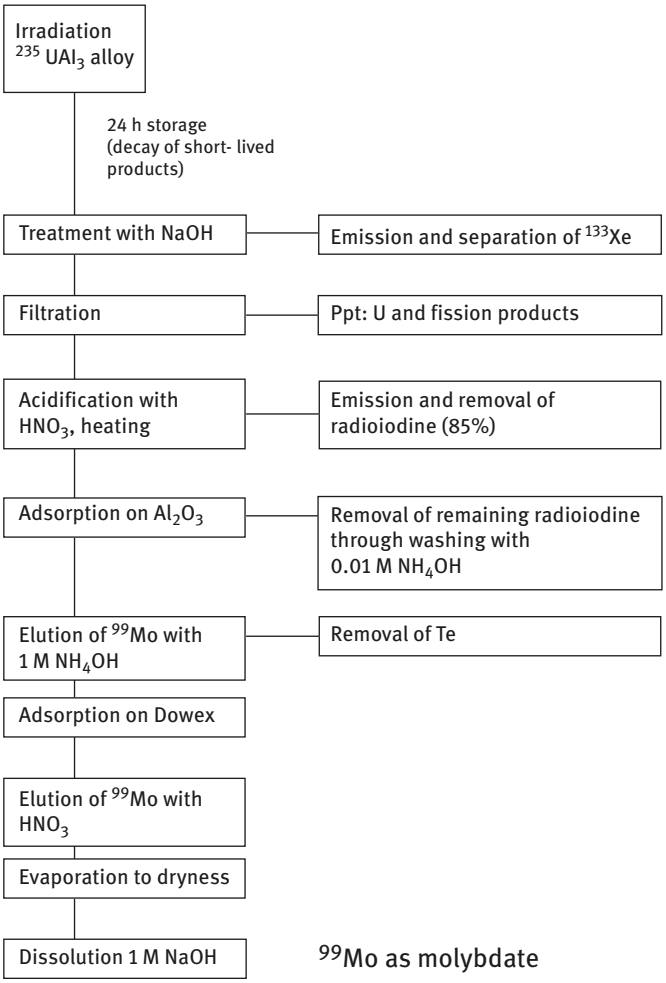

Fig. 5.2: Flow sheet of the separation procedure for ^{99}Mo from fission products, formed in irradiation of $^{235}UAl_3$ alloy in a nuclear reactor.

separation technology has been established at a few specialised reactor cites around the world, and nca ^{99}Mo of high purity (total γ-ray emitting impurity <100 ppm; total ^{90}Sr impurity < 0.06 ppm; total α-ray emitting impurity < 0.001 ppm) is achieved in TBq quantities. It is then used for preparing generators, that is, loading Al_2O_3 columns with ^{99}Mo. In general, the fission-produced ^{99}Mo on an Al_2O_3 column is regarded as a gold standard generator system.

The elution of ^{99m}Tc, formed in the decay of ^{99}Mo and adhering to the column, is done by saline. The eluted ^{99m}Tc then exists as pertechnetate. The eluted solution is transferred to an ampoule containing an appropriate lipophilized mixture of reagents. On shaking, the labelling of given ligands with ^{99m}Tc occurs in a specific configuration and the product is then ready for human use.

The ease and success associated with the generator elution of ^{99m}Tc and the development of kit formulation of some very important ^{99m}Tc-labelled diagnostic agents has led to very wide use of ^{99m}Tc. As mentioned earlier, the fission ^{99}Mo is produced only at a few advanced centres and is then distributed to various laboratories around the world where the generator loading is undertaken (*dispensing*). The generators are then sent to regional clinics. It is estimated that worldwide 40 million patients per year are subjected to diagnostic investigations with ^{99m}Tc. Another estimate suggests that more than 70% of all nuclear medical diagnostic investigations are performed using this radionuclide. Despite this success story and the demonstrated need for continuous availability of this radionuclide, its future supply appears to be somewhat jeopardized. On one hand the presently used reactors are ageing and new facilities are coming up only slowly and, on the other, there is a risk of nuclear weapons´ proliferation due to the use of HEU as the target material. Both these aspects demand a search for alternative methods of production and separation of ^{99}Mo and/or ^{99m}Tc. Considerable efforts are underway in this direction. A brief discussion is given below.

Recent Developments Regarding Supply of ^{99m}Tc

Recent developments relate to both reactor and non-reactor production of the parent ^{99}Mo or direct production of ^{99m}Tc. As far as *reactor production* is concerned, four points are of current interest: *proliferation risk, problem of specific activity, efficient use of existing reactors* and *development of new facilities*.

- With regard to proliferation risk, a few production centres have started modifying the irradiation target using low-enriched ^{235}U (LEU) and adjusting the incumbent chemical processing. Due to handling of increased volumes, the costs will go up, but they have to be taken into account. As of August 2018, it was reported that the Reactor Centre at Petten (The Netherlands) has become the first ^{99}Mo production facility in Europe to use LEU.
- As far as the specific activity is concerned, efforts are underway to develop better ^{99}Mo/^{99m}Tc generator systems which could make use of ^{99}Mo produced

via the $^{98}Mo(n,\gamma)^{99}Mo$ reaction during irradiation of ^{nat}Mo in a nuclear reactor. The company NorthStar Medical Radionuclides, USA, is currently finalizing this ^{99}Mo production method using the University of Missouri Research Reactor. Several other companies are also working in this direction.

- The risk in the supply of this crucial medical radionuclide has led to better co-operation between the production centres involved as well as partial utilization of even some research reactors which were hitherto not used for irradiations for medical radionuclide production (e.g., the FRM-II in Munich, Germany). A high-level working group of the Nuclear Energy Agency in Paris is continuously monitoring the developments. A recent analysis (2017) suggests that the level of ^{99}Mo supply capacity is adequate till 2022.
- As far as new reactor facilities for ^{99}Mo production are concerned, it is known that medium-flux reactors are reaching completion in Australia, China and South Korea. They are expected to be operational to produce large quantities of ^{99}Mo within about 5 years´ time. Plans are also underway in Russia to produce fission ^{99}Mo in large quantities. Thus the situation is not as bleak as some analysts put it. Nonetheless, a vigilant watch on the supply chain of ^{99}Mo is necessary and continuous developments are needed for assuring its secure supply.

The *non-reactor production* of $^{99}Mo/^{99m}Tc$ has been extensively investigated, mostly in Canada, where the supply chain was in special danger due to the planned shutdown of the two nuclear reactors at Chalk River serving as the major producers of ^{99}Mo. In general, more use of accelerators has been proposed [145]. Several nuclear routes using accelerators have been investigated (for a review cf. [72]). However, most of those studies deal with reaction cross-section measurements. Only the direct production of ^{99m}Tc via the $^{100}Mo(p,2n)^{99m}Tc$ reaction has been technically investigated in some detail. The theoretical yield of ^{99m}Tc over the energy range $E_p = 22 \rightarrow 10$ MeV calculated from the evaluated excitation function [73] of this reaction amounts to 700 MBq μAh^{-1}. This yield is sufficient for production purposes and the method is therefore being commercially developed in Canada. A new type of 24 MeV cyclotron has been developed and a network of several centres is being established. Different types of solid targets containing enriched ^{100}Mo, prepared via pressing, rolling, electroplating, electrophoretic deposition or making a $^{100}Mo_2C$ alloy, have been used in irradiations with protons at low to medium currents. The radiochemical separation of ^{99m}Tc has been done mainly using thermochromatography as described in Section “Thermochromatography” in Chapter 4 (see Fig. 4.2), or partly via wet chemical methods [146]. A radiochemical purity of 99.7% of the final pertechnetate $[^{99m}Tc]TcO_4$ solution has been demonstrated and this meets the same USP requirements as for the $^{99}Mo/^{99m}Tc$ generator produced pertechnetate. By irradiating a ^{100}Mo target with 22 MeV protons at 400 μA for 6 h, after chemical separation,

a batch yield of about 1 TBq of ^{99m}Tc was achieved [146]. There are, however, two open points: (a) the radionuclidic purity of the product when <100% enriched ^{100}Mo target is used, and (b) tolerable limits of the metals ^{99g}Tc and ^{98}Tc in the pertechnetate. The estimated values of those stable isotopes may be up to a factor of 2 higher than in the generator-produced ^{99m}Tc eluted at 24 h intervals [73].

The cyclotron production of ^{99m}Tc via the ^{100}Mo(p,2n)^{99m}Tc reaction thus appears to be viable provided the long-lived impurities are well investigated. The production would solve local or at the best regional problems. It would, however, involve daily intensive production efforts and good logistics. It will not be as conveniently available as from a generator system. The product would probably be expensive and technologically beyond the reach of developing countries. For meeting international demands, the supply of generators utilizing the fission-produced ^{99}Mo may therefore remain indispensable.

^{123}I ($T_{½}$ = 13.2 h)

For the production of the radionuclide ^{123}I about 25 nuclear processes have been investigated (for early reviews, see Appendices I and II). Originally, the ^{124}Te(p,2n)^{123}I reaction using a 99% enriched $^{124}TeO_2$ target over the energy range E_p = 26 → 23 MeV was very popular. It is a high-yield process but the level of the ^{124}I impurity is rather high. Today, only three reactions are used. On a small cyclotron (Level III cyclotron), the reaction ^{123}Te(p,n)^{123}I over the energy range E_p = 14 → 10 MeV is utilized, provided a highly enriched $^{123}TeO_2$ target is available. The yield of ^{123}I is, however, rather low. The separation of radioiodine is generally done via a dry distillation technique and the target can be repeatedly used without any further processing (see Chapter 4). The second method involves the use of ^{124}Xe gas as target material to produce the precursor ^{123}Xe ($T_{½}$ = 2.1 h) which decays to ^{123}I. It demands a medium-sized cyclotron (E_p ≈ 30 MeV, Level IV). Starting with 99.8% enriched ^{124}Xe gas, the precursor ^{123}Xe is produced via the processes ^{124}Xe(p,2n)^{123}Cs → ^{123}Xe and ^{124}Xe(p,pn)^{123}Xe (see Chapter 2). Over the optimum energy range of E_p = 29 → 23 MeV, the major contribution to the formation of ^{123}I is furnished by the (p,2n) process. The activated xenon is allowed to decay for about 7 h and then it is cryogenically removed from the vessel. Thereafter, the decay product ^{123}I deposited on the inner wall of the container is collected by rinsing. This method of production is now commonly used because it gives the purest product and is the only one accepted by regulations in most countries. The enriched target gas ^{124}Xe is very expensive. The technology related to irradiation and safe recovery of the target gas as well as an efficient removal of ^{123}I from the target wall is thus very demanding. Nonetheless, the technology has been well developed at Karlsruhe (Germany) and Vancouver (Canada). It is now commercially available. The third method of production of ^{123}I utilizes the intermediate energy nuclear process ^{127}I(p,5n)^{123}Xe → ^{123}I, the

optimum energy range being E_p = 65 → 45 MeV. The product ^{123}Xe is removed from the NaI target, mostly by online sweeping with a He stream (see Fig. 8 in Appendix II). It is then collected in a cooled vessel and is allowed to decay for about 7 h. Thereafter, ^{123}I is obtained in a small volume by rinsing the inner wall of the vessel. This process leads to a high yield of ^{123}I but in this case the product contains about 0.25% ^{125}I ($T_{½}$ = 59.4 d) as impurity.

The radioiodine produced by all the three methods occurs as iodide, which is a suitable chemical form for subsequent labelling of organic compounds via substitution reactions. With some shortage of ^{99m}Tc and the buildup of a network of 24 MeV cyclotrons, especially in Canada, it is predicted that the use of ^{123}I would increase. The most convenient reaction to produce high-purity ^{123}I at those machines would be the ^{123}Te(p,n)^{123}I process described earlier. However, a high enrichment target (~99%) would be needed.

^{201}Tl ($T_{½}$ = 3.06 d)

The production of ^{201}Tl is mainly done via the route $^{203}\mathrm{Tl}(\mathrm{p},3\mathrm{n})^{201}\mathrm{Pb} \xrightarrow[16.9\mathrm{h}]{\mathrm{EC}} {}^{201}\mathrm{Tl}$, utilizing the energy range E_p = 28 → 20 MeV. The irradiation of ^{nat}Tl or >96% enriched ^{203}Tl is done at a medium-sized cyclotron (Level IV) using an electrolytically deposited target. Since high current proton beams are used, a slanting target is preferred. The chemical processing follows in two steps: first, the precursor ^{201}Pb ($T_{½}$ = 9.4 h) is separated and, after its decay to ^{201}Tl, the product is isolated as ^{201}TlCl. The precursor ^{201}Pb (together with other lead radionuclides, e.g., ^{203}Pb) is separated from ^{nat}Tl or ^{203}Tl target (which is then reused) and other radiocontaminants by adsorption on $Fe(OH)_3$ ppt, followed by its removal from Fe carrier via anion-exchange chromatography. Thereafter, nca ^{201}Pb is allowed to decay in a solution of HCl for 32 h and the daughter radionuclide formed is reduced by hydrazine to $^{201}Tl^{1+}$. Finally, the separation of nca $^{201}Tl^{1+}$ from the nca ^{203}Pb is performed via anion-exchange chromatography [147]. This method with some modifications is still used in large-scale production of ^{201}Tl.

It should be pointed out here that the target material thallium is toxic. The product ^{201}Tl, however, is in nca form and can be safely used, provided the stringent quality control standards are fully complied with. These include tests on radionuclidic and chemical purity, in the latter case specially on the inactive Tl and hydrazine levels. Furthermore, ^{201}Tl is useful only in the monovalent form; the trivalent form is not effective for medical application.

^{67}Ga ($T_{½}$ = 3.26 d) and ^{111}In ($T_{½}$ = 2.81 d)

These two less commonly used SPECT radionuclides are generally produced at a medium-sized cyclotron using the nuclear reactions ^{68}Zn(p,2n)^{67}Ga and ^{112}Cd(p,2n)^{111}In on 98.5% enriched targets over the optimum energy range of E_p = 25 → 18 MeV. At low-

energy cyclotrons, the low-yield reactions ^{67}Zn(p,n)^{67}Ga and ^{111}Cd(p,n)^{111}In on 90–95% enriched targets have also found some local use but for large-scale commercial production, the (p,2n) reaction is the method of choice for both the radionuclides.

The enriched ^{68}Zn or ^{112}Cd target is prepared by electroplating on a Cu plate, or simply the powder is pressed to form a pellet. High-current irradiations are generally done using a slanting beam. The chemical processing of the irradiated target is done by using two different methods, namely ion-exchange chromatography or solvent extraction, thereby the enriched target material is also recovered. The two radionuclides are commercially available in GBq amounts. The nca radionuclide ^{67}Ga is generally made available as gallium citrate. The nca radionuclide ^{111}In, on the other hand, is usually supplied as [^{111}In]$InCl_3$. In both cases, a stringent test of the non-radioactive metallic impurities, like Cu, Fe and Al is performed.

It is pointed out that the use of ^{67}Ga and ^{111}In as SPECT agents is declining. However, since they emit a large number of Auger electrons, they are now partly being considered for Auger therapy. In particular, ^{111}In is attracting more attention. The demand on its radionuclidic and chemical purity is thus increasing.

Other γ-Ray Emitters

A few other γ-ray emitters have also found some diagnostic application or are of potential interest for use as SPECT agents. To the former group belongs the generator system ^{81}Rb/^{81m}Kr, which delivers the short-lived γ-ray emitter ^{81m}Kr ($T_{½}$ = 13.1 s, E_γ = 190 keV, I_γ = 67%) for application in lung ventilation studies. The production of the parent radionuclide ^{81}Rb is carried out at a cyclotron via the nuclear reaction ^{82}Kr(p,2n)^{81}Rb at E_p = 25 → 20 MeV. For this purpose, a Kr gas target is used and the rubidium activity is collected by rinsing the target with water (cf. Chapter 3). Clinical-scale yields are easily obtained. Some of the potentially useful SPECT radionuclides are discussed in Chapter 6.

5.3 Standard Positron Emitters for PET

For routine diagnostic investigations using PET, mainly the short-lived positron emitters of organic elements, viz. ^{11}C ($T_{½}$ = 20.4 min) and ^{18}F ($T_{½}$ = 109.8 min), and to a lesser extent ^{15}O ($T_{½}$ = 2.0 min) and ^{13}N ($T_{½}$ = 10.0 min), are used. They are all produced at a small-sized cyclotron, generally Level III machine. The radionuclides ^{11}C, ^{13}N and ^{15}O are mainly used at the site of production. The radionuclide ^{18}F, on the other hand, is extensively employed for transport to nearby medical units having a tomograph but not a cyclotron. A large variety of compounds of those organic radionuclides have been developed for clinical use. Besides those four positron emitters, two other short-lived positron emitters, namely ^{68}Ga ($T_{½}$ = 1.15 h) and

^{82}Rb ($T_{½}$ = 1.3 min), are also widely used in diagnostic studies. A large number of nuclear reactions have been investigated for the production of the above-mentioned six standard positron emitters (for early reviews, see Appendices I and III). Over the years, however, for each radionuclide just one or two most suitable production methods have been developed.

5.3.1 Direct Production of Standard Positron Emitters

The excitation functions of nuclear reactions used for the formation of the four organic positron emitters generally show strong fluctuations or resonances, probably due to the population of known discrete levels of the product nucleus. The evaluated data for the more commonly used reactions are available [53] and a later detailed study on the ^{18}O(p,n)^{18}F reaction [61] has been described in Chapter 2 (cf. Fig. 2.9). The integrated yields of the products calculated from the excitation functions, however, show smooth curves, that is, in the production process the nuclear structure effects are washed out. The common methods of production of the four standard organic positron emitters are summarized in Table 5.3. The thick target yields were taken from ref. [53], except for the ^{18}O(p,n)^{18}F reaction, where the yield was calculated from the data given in ref. [61]. Since this is the most important reaction from the point of view of standard PET technology, the integrated yield for a saturation irradiation was also calculated from the two known extensive measurements [60, 61]. The results are shown in Fig. 5.3. The information should be useful in large-scale production of ^{18}F. The radionuclides ^{11}C, ^{13}N and ^{18}F are easily produced using a proton beam from a low-energy cyclotron. For ^{15}O production

Table 5.3: Common methods of production of short-lived organic positron emitters.

Nuclide	$T_{½}$ (min)	Production route	Energy range (MeV)	Thick target yield[a] (MBq μA h^{-1})	Target	In-target product	Typical batch yield (GBq)
^{11}C	20.4	^{14}N(p,α)	13 → 3	3820	$N_2(O_2)$	^{11}CO, $^{11}CO_2$	>100
^{13}N	10.0	^{16}O(p,α)	16 → 7	1665	$H_2{}^{16}O$	$^{13}NO_2^-$, $^{13}NO_3^-$	30
^{15}O	2.0	^{14}N(d,n)	8 → 0	2368	$^{14}N_2(O_2)$	$[^{15}O]O_2$	100
		^{15}N(p,n)	10 → 0	2220	$^{15}N_2(O_2)$	$[^{15}O]O_2$	80
^{18}F	109.8	^{18}O(p,n)	16 → 3	3893	$H_2{}^{18}O$	$^{18}F_{aq}^-$	150
					$^{18}O_2/(F_2)$	$[^{18}F]F_2$	40
		^{20}Ne(d,α)	14 → 0	1110	$Ne(F_2)$	$[^{18}F]F_2$	25

[a] Calculated from the respective excitation function [53, 61], assuming 100% enrichment of the target isotope for an irradiation time of 1 h.

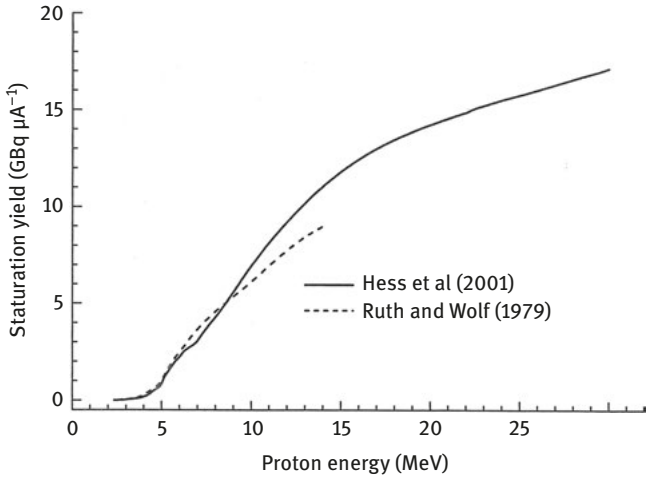

Fig. 5.3: Thick target saturation yield of ^{18}F via the $^{18}O(p,n)^{18}F$ reaction calculated from the comprehensive data reported in refs. [60, 61], taken from Hess et al. [61], with courtesy of De Gruyter.

via the $^{14}N(d,n)$ reaction, and for electrophilic ^{18}F production via the $^{20}Ne(d,\alpha)$ reaction, however, deuterons of energy about 10 MeV are needed. On the other hand, for the production of ^{15}O, in a few PET centres a small single particle cyclotron ($E_d < 4$ MeV) has also been successfully utilized (see Chapter 1).

Extensive cooperative work was carried out in the late 1980s on the development and standardisation of production methods of short-lived β^+ emitters, with the involvement of about 15 laboratories from Western Europe under a COST action of the European Union. The details of the production routes were published [115]. In the meantime further progress has been achieved. In the case of ^{11}C and ^{15}O, generally high-pressure gas targets in batch mode are used (cf. Chapter 3). The product activity is removed from the target by simple expansion and led to vessels where conversion to other chemical forms (known as precursors) suitable for labelling of organic compounds is done. The chemical form of the activity leaving the target depends upon the additive given to the N_2 gas in the target and in the case of ^{11}C, also on the radiation dose effective in the target. The resulting ^{15}O from an $N_2(O_2)$ target, for example, is $[^{15}O]O_2$. In the case of ^{11}C production, at high radiation doses mostly $^{11}CO_2$ is formed. The production of both ^{11}C and ^{15}O is rather simple, and GBq quantities are easily obtained [148]. However, in the production of high specific activity ^{11}C, special precautions regarding gas composition, construction material and chemicals are needed since stable ^{12}C is present everywhere [149]. The most reliable production of ^{15}O demands a deuteron beam at the cyclotron. If it is not available, the (p,n) reaction on >99% enriched ^{15}N is utilized. However, an efficient recovery system for the enriched target gas must then be incorporated in the system.

An important consideration in the production of both ^{11}C and ^{15}O is the *level of the radioactive impurity* present in the gas stream released from the target. A full production batch of ^{11}C at the end of an irradiation, for example, contains about 20% ^{14}O ($T_{1/2}$ = 70 s) and 5% ^{13}N ($T_{1/2}$ = 10 min) as impurities, as calculated from the excitation functions (see Appendix VII). This must be taken into account while estimating the batch yield of ^{11}C formed. The short-lived ^{14}O decays out during the synthesis of ^{11}C-labelled products but the disposal of ^{13}N in the waste must be considered. Similarly in the production of ^{15}O via deuterons on N_2 gas, the reactions $^{14}N(d,t)^{13}N$ and $^{14}N(d,\alpha n)^{11}C$ also occur (cf. Chapter 2). The ratio of the activities at end of bombardment (EOB) ($^{13}N/^{15}O$ and $^{11}C/^{15}O$) was calculated from the respective excitation function and the results are shown in Fig. 5.4 [63]. Obviously, at $E_d \approx 10$ MeV, the contribution of ^{13}N increases to about 0.4% of the ^{15}O activity. This was experimentally confirmed by gas chromatographic analysis of a few samples taken from the gas stream coming out of the target [63]. The presence of ^{13}N itself is not very critical but the other product of the contributing (d,t) reaction, namely tritium, must be controlled while disposing off the wastewater. Its content will be higher if the deuteron energy is above 10 MeV.

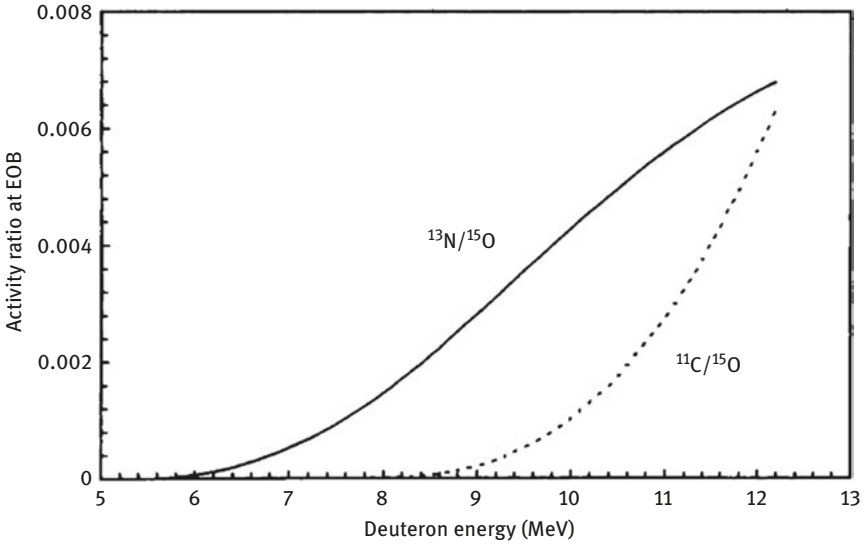

Fig. 5.4: Activity ratio of $^{13}N/^{15}O$ and $^{11}C/^{15}O$ (at EOB) as a function of deuteron energy on the N_2 target gas, taken from Szücs et al. [63], with courtesy of De Gruyter.

The production of *electrophilic ^{18}F* is also carried out using a gas target. However, the removal of the activity from the target demands addition of some F_2 carrier. In the case of the $^{20}Ne(d,\alpha)^{18}F$ reaction, the F_2 (0.1–0.2%) carrier is added directly to

the neon gas target. The method was first developed at the Brookhaven National Laboratory. Later many groups contributed [115]. Both the yield and the specific activity of $[^{18}F]F_2$ are limited, especially if the maximum deuteron energy available at the medical cyclotron is only about 9 MeV. While using the $^{18}O(p,n)^{18}F$ reaction on 98% enriched $^{18}O_2$ gas, however, a two-step irradiation is necessary [150]. Optimisation studies show that the yield and the specific activity of the ^{18}F obtained are higher in the case of the $^{18}O(p,n)$ reaction [121, 150, 151]. A correlation between the added F_2-carrier and the specific activity of ^{18}F [121] is given in Fig. 5.5. In general, under optimum conditions, the $[^{18}F]F_2$ yield amounts to 25 GBq and its specific activity is <0.6 TBq mmol^{-1} (now termed as *molar activity*). In many cases, the achieved specific activity may be sufficient. However, it is still about a factor of 50 lower than that needed in preparation of several radiopharmaceuticals, for example, ^{18}F-labelled neuroreceptor ligands.

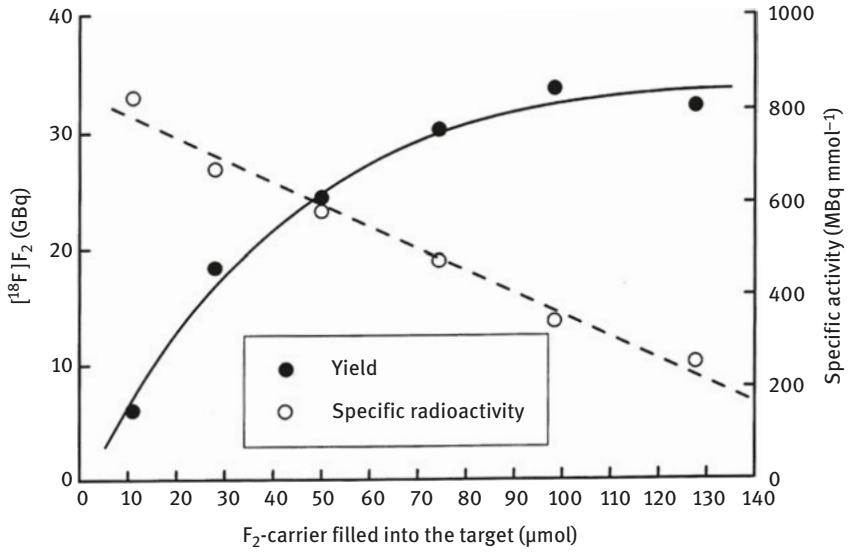

Fig. 5.5: Yield and specific activity of $[^{18}F]$fluorine as a function of fluorine carrier, 30 min after the end of the activation irradiation, taken from Hess et al. [121], with permission from Elsevier.

The radionuclides ^{13}N and *nucleophilic* ^{18}F are commonly produced using water targets, and several types of water targets have been developed, particularly for ^{18}F production. In many laboratories, intermediate pressure (up to 7 bar) targets are used, which can withstand 17 MeV proton beam currents of up to 20 μA (cf. Fig. 3.4). High-pressure (>10 bar) water targets can withstand beam currents of up to about 50 μA. After the end of the irradiation, the water is transferred from the target by a He-driven pressure of 1.3 bar to a hot cell. This is done through

a polyethylene–polypropylene copolymer tube with an i.d. of 0.8 mm. The transfer over 40 m through this tubing takes only 2 min, and >90% of the product activity is recovered. The same target can be used for the production of both ^{13}N and ^{18}F. In the former case, natural water ($H_2{}^{16}O$) is used and in the latter case >95% enriched water ($H_2{}^{18}O$). In high-current irradiations, the resulting products are $^{13}NO_3^-$ and $^{18}F^-_{aq}$, respectively. In the latter case, the recovery of the enriched water is essential. This is commonly achieved by transferring the irradiated water to an ion-exchange bed whereby the ^{18}F activity is adsorbed, and the enriched water passes through and is collected. The ^{18}F activity is removed from the column by washing it with 0.1 M solution of Na_2CO_3, and the batch yield amounts to about 75 GBq for intermediate pressure targets and up to 150 GBq for high-pressure targets. Occasionally, separation of $^{18}F^-$ from the irradiated $H_2{}^{18}O$ is also done electrolytically [140]. The defluorinated target water is removed from the electrolytic cell by a gentle stream of helium, and the release of $^{18}F^-$ from the electrode is affected using a suitable solvent and a low-strength electric field (see Chapter 4).

Continuous developments are underway to increase the batch yield of ^{18}F for producing the most commonly used radiopharmaceutical [^{18}F]-2-fluoro-2-deoxy-D-glucose on an industrial scale. Furthermore, because of the high specific activity of $^{18}F^-_{aq}$, some attempts are also being made to convert it to high specific activity electrophilic ^{18}F, which is needed for the synthesis of a few radiopharmaceuticals. The yield achieved so far is, however, low. Therefore, a high starting $^{18}F^-_{aq}$ activity is required.

The radionuclidic and chemical purities of all four organic positron emitters obtained after the purification steps are generally >99%. If proper production conditions are observed, the radiochemical purity and the specific activity are also satisfactory. Thus, the production technology of the four standard PET radionuclides is well established.

5.3.2 Generator-Produced Standard Positron Emitters

Two commonly used positron emitters, namely ^{68}Ga ($T_{½}$ = 1.15 h) and ^{82}Rb ($T_{½}$ = 1.3 min), are obtained through generator systems, that is, through the decay of their parent radionuclides ^{68}Ge ($T_{½}$ = 271.0 d) and ^{82}Sr ($T_{½}$ = 25.3 d), respectively. They find application mostly in PET studies at centres without a cyclotron. The β^+ emitter ^{68}Ga is widely used for PET attenuation correction and, in recent years with increasing tendency, for labelling molecules which find significant applications in assessment of blood–brain barrier integrity as well as in tumour localisation. It is an ideal metallic PET radionuclide due to its suitable half-life and chemical properties. Some radiopharmacists believe that if suitable labelled compounds are developed, this radionuclide may compete with or even replace ^{18}F. The β^+ emitter ^{82}Rb finds application in cardiac PET, with several objectives, for example, myocardial imaging, investigation of myocardial viability and non-invasive diagnosis of coronary artery disease.

^{68}Ge/^{68}Ga Generator System

For the production of the parent radionuclide ^{68}Ge, nine nuclear processes were investigated (see Appendix III). However, only two from them found practical application. They include spallation of As or Br and ^{nat}Ga(p,xn)^{68}Ge. Earlier, the method of choice was the spallation process and the radionuclide was exclusively produced at large accelerators where long irradiations in parasitic positions were possible. The purification of the product involved multistep wet chemical processing. The ^{nat}Ga(p,xn)^{68}Ge method was investigated by irradiating a Ga_4Ni alloy with 20 MeV protons and radiogermanium was separated via solvent extraction [152]. Despite the relatively high current of 45 μA and irradiation time of 60 h, the product batch yield was relatively low (<2 GBq), mainly due to the low energy of the protons used. Later cross-section measurements showed that the useful part of the excitation function of this nuclear process extends to energies up to 50 MeV and even beyond, because both ^{69}Ga and ^{71}Ga contribute to the formation of ^{68}Ge (see Fig. 8 in Appendix V). Therefore, in recent years, with the availability of modern accelerators that deliver 70–100 MeV proton beams, the use of the (p,xn) reaction has received enhanced attention. The target for irradiation generally consists of gallium metal encapsulated in niobium. Long irradiations with 100 MeV protons were carried out at BNL [153]. After a waiting time of several weeks to allow short-lived products to decay, wet chemical processing was done and radiogermanium was extracted as $GeCl_4$ in toluene or benzene. Further purification of ^{68}Ge (especially from ^{65}Zn) was performed by several extraction and back-extraction cycles. The batch yield of ^{68}Ge corresponded to about 18 GBq and its radionuclidic purity was >99%. The level of stable metal impurities was generally below 1 ppm. From the excitation function, a suitable energy range for ^{68}Ge production via this route appears to be $E_p = 70 \rightarrow 20$ MeV.

For preparing the ^{68}Ge/^{68}Ga generator system, the separated ^{68}Ge is generally loaded on a column, filled with tin oxide, titanium oxide or an organic resin, and the positron emitting daughter ^{68}Ga is periodically removed by elution with 0.01-1 M HCl. In recent years, considerable methodological development has followed on this generator to improve its performance (e.g., minimisation of breakthrough, improvement in elution yield and concentration of the eluate). Extensive work has led to a very efficient processing of the ^{68}Ga-eluate for medical application [154]. In view of the increasing importance of ^{68}Ga in labelling molecules for PET studies [155], this methodology holds good promise.

^{82}Sr/^{82}Rb Generator System

For the production of the parent radionuclide ^{82}Sr, six nuclear processes were investigated (cf. Appendix III). In later years, some further detailed studies on those processes were performed. Initially, similar to ^{68}Ge, for the production of this

radionuclide as well the Mo(p,spall)^{82}Sr process was extensively used, mainly at Los Alamos. The major drawback of the process was the presence of large amount of ^{85}Sr ($T_{½}$ = 64.9 d) in the separated ^{82}Sr. In later years, the emphasis got shifted to the ^{85}Rb(p,4n)^{82}Sr reaction. On the other hand, for practical application the use of the ^{nat}Rb(p,xn)^{82}Sr process was found to be more convenient and economical (by avoiding the enriched material). The excitation function of this nuclear process is given in Fig. 2.18 together with that of the competing process ^{nat}Rb(p,xn)^{85}Sr [95]. The suitable energy range for the production of ^{82}Sr is E_p = 70 → 50 MeV. The target for irradiation generally consists of RbCl encapsulated in stainless steel. Typical irradiation time with 70 MeV protons is about a week at 50 μA [156]. The wet chemical processing of the irradiated target is generally started about 1 week later and is based on ion-exchange chromatography. Batch yields of up to 70 GBq ^{82}Sr have been reported from BNL and iThemba LABS.

The level of the ^{85}Sr impurity in ^{82}Sr is considerably reduced while using ^{nat}Rb(p,xn)^{82}Sr nuclear process in comparison to the spallation route. However, a control of the effective projectile energy range within the target is essential. Figure 5.6 shows the calculated yields of both ^{85}Sr and ^{82}Sr as a function of proton energy on a RbCl target [95]. The ratio of the two activities was calculated from the excitation functions and also measured experimentally for various energy ranges. The results are given in Table 5.4. In order to keep the ^{85}Sr/^{82}Sr ratio below 0.25, it is recommended that the lower energy limit should not be below 40 MeV. A very suitable energy range for the production of ^{82}Sr via this route appears to be E_p = 70 → 50 MeV.

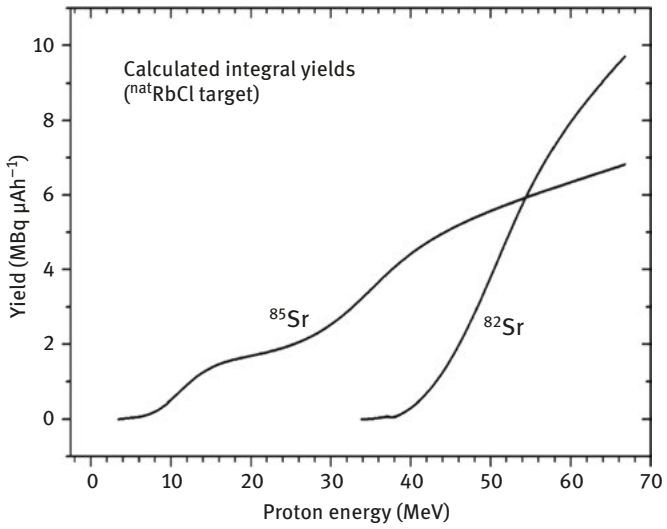

Fig. 5.6: Integral yields of ^{85}Sr and ^{82}Sr in proton irradiation of ^{nat}RbCl, calculated from the excitation functions; taken from Qaim et al. [95], with permission from Elsevier.

Table 5.4: Ratio of $^{85}Sr/^{82}Sr$ activity in proton irradiation of $^{nat}RbCl^{*}$.

Energy range (MeV)	Ratio $^{85}Sr/^{82}Sr$ [a]	
	Calculated [b]	Experimental
65 → 44	0.21	0.18
60 → 37	0.27	0.24
55 → 30	0.57	0.44
50 → 21	1.01	0.82
45 → 10	3.03	2.77

[*] Adapted from Qaim et al. [95], with permission from Elsevier.
[a] All values extrapolated to EOB.
[b] Calculated from the excitation functions for 1h irradiation.

For preparing the $^{82}Sr/^{82}Rb$ generator system, the separated ^{82}Sr is loaded on a suitable column (e.g., Chelex 100 chelating resin, Dowex-1 anion exchanger and Purolite S950) and purged with an eluent, generally a large volume of saline. The daughter ^{82}Rb is then periodically removed by elution with saline. It should be pointed out that the level of ^{85}Sr in ^{82}Sr affects the quality of the generator. In case of strontium breakthrough from the column, the amount of ^{85}Sr in the eluted ^{82}Rb is difficult to measure because its characteristic γ-ray peak at 514 keV cannot be easily distinguished from the 511 keV annihilation peak of the β^{+} emitter ^{82}Rb. Thus, a constant watch on the level of ^{85}Sr as well as on the integrity of the column is necessary.

In order to assure a reliable and continuous supply of this generator system, a consortium of laboratories around the world collaborates in irradiations of rubidium targets. They are then all transported to Los Alamos where the chemical processing is done. The purified ^{82}Sr is then distributed worldwide to prepare generators.

5.3.3 Concluding Remarks about Standard Positron Emitters

In recent years, PET imaging has been gaining enhanced significance (see Appendix VI) because it leads to quantitative information on regional physiological and pharmacological activities by a molecular probe (labelled with a positron emitter) with high sensitivity and with a spatial resolution down to 1 mm. The major impetus came through the production of ^{18}F in large quantities via the $^{18}O(p,n)^{18}F$ reaction at a small cyclotron followed by a simplified method of nucleophilic substitution by ^{18}F in organic molecules, developed at the Forschungszentrum Jülich. This led to an easy preparation of the most frequently used PET-tracer 2-[^{18}F]-fluoro-2-deoxy-D-glucose in large amounts. This radiopharmaceutical is now extensively used in neurology, cardiology and oncology. It is estimated that worldwide about 5 million

patients per year undergo diagnostic investigations using this radiopharmaceutical. Today, the whole PET technology (consisting of a Level III cyclotron, radionuclide production unit and automated radiosynthesis apparatus) is commercially available. As mentioned in Chapter 1 (Section "General: Classification of Cyclotrons") presently worldwide about 1000 Level III cyclotrons are either being installed or manufactured for PET applications in medicine. This technology is thus proliferating and is reaching even remote corners of the world.

A second approach involving diagnostic studies via PET is based on the utilization of the two generator-produced positron emitters ^{68}Ga and ^{82}Rb, mainly at centres that have no access to a cyclotron. The two generator systems are also now commercially available and their use is being established even in many parts of the world. In particular, the use of ^{68}Ga-labelled pharmaceuticals is expanding at a rapid pace. In some laboratories with a cyclotron even the direct production of this radionuclide is being investigated.

5.4 Standard β^- Emitters for Internal Radiotherapy

Among the large number of known β^- emitters for therapy, about 20 are of more interest. Some of the criteria for their choice are given in Appendix IV (see also contribution by Zalutsky in ref. [25]). The seven most commonly used ones are considered as "standard β^--emitting radionuclides" and their production routes are given in Table 5.5.

The β^--emitters ^{32}P and ^{90}Y have rather high β^- energies (cf. Table 1.1) and are used in palliative therapy. They are introduced into joints and cavities as gels or microspheres. The radionuclide ^{32}P also finds application in labelling of nucleotides. Another variation of internal therapy with β^- emitters involves the radiosynthesis of tumour-seeking agents. For this purpose, ^{89}Sr, ^{153}Sm, ^{177}Lu, ^{188}Re and ^{131}I are more commonly used. In particular, the trivalent metals are finding increasing use in treatment of bone metastases. For example, ^{177}Lu attached to peptides is used for the treatment of prostate cancer. Similarly, ^{188}Re forms a variety of chelates which are of great potential interest in medicine. The radionuclide ^{131}I in the form of iodide is extensively applied in treatment of thyroid tumours. In fact, ^{131}I is by far the most important therapeutic radionuclide, having an established place in the management of follicular thyroid carcinoma.

^{32}P ($T_{½}$ = 14.3 d)

The radionuclide ^{32}P is produced via the neutron threshold reaction ^{32}S(n,p)^{32}P. In fact, this was the reaction originally used by Chiewitz and Hevesy to produce this first medical radionuclide utilizing a Ra/Be neutron source (see Chapter 1). The cross section of the reaction averaged over the fission neutron spectrum is smaller than that for a Ra/Be neutron spectrum. Nonetheless, due to much higher neutron

Table 5.5: Common methods of production of standard β^- emitters for internal therapy.

Radionuclide	$T_{1/2}$	Production route	Cross section	Target material	Typical experimental batch yield (GBq)
^{32}P	14.3 d	^{32}S(n,p)	68 mb [a]	^{32}S (powder, pellet or melted)	100
^{89}Sr	50.5 d	^{89}Y(n,p)	0.31 mb [a]	Y_2O_3 pellet	20
^{90}Y	2.7 d	^{90}Sr→^{90}Y (generator)	FY = 5.77% [b] (^{90}Sr)	$^{90}SrCl_2$ (solution) [f]	<5 (per generator)
^{131}I	8.02 d	^{235}U(n,f)	FY = 2.88% [b] (^{131}I)	$^{235}UAl_3$	>10^3
		^{130}Te(n,γ)^{131m,g}Te $^{131m,g}Te \xrightarrow{\beta^-} {}^{131}I$	204 mb [c]	Te metal, TeO_2	600–800
^{153}Sm	1.93 d	^{152}Sm(n,γ)	σ_{th}: 213 b I_o: 2940 b FS: 70 mb [d]	Sm_2O_3, $^{152}Sm_2O_3$ (enriched)	20
^{177}Lu	6.65 d	^{176}Lu(n,γ)	σ_{th}: 2097 b I_o: 919 b [d]	$^{176}Lu_2O_3$ (enriched)	800
		^{176}Yb(n,γ)^{177}Yb $^{177}Yb \xrightarrow{\beta^-} {}^{177}Lu$	σ_{th}: 2.81 b I_o: 6.8 b [d]	$^{176}Yb_2O_3$ (enriched)	8
^{188}Re	17.0 h	^{187}Re(n,γ)	σ_{th}: 74.5 b I_o: 314 b FS: 117 mb [d]	Re_2O_7	50
		^{186}W(n,γ)^{187}W	σ_{th}: 36.5 b I_o: 290 b [e]	W metal, WO_3	
		^{187}W(n,γ)^{188}W	σ_{th}: 14.5 b I_o: 398 b [e]		20 (^{188}W)
		^{188}W→^{188}Re (generator)		[^{188}W]tungstate (on Al_2O_3)	<5 (per generator)

[a] Fission neutron spectrum-averaged cross section (FS), taken from [42].
[b] Fission yield (%).
[c] Thermal neutron capture cross section.
[d] Cross section for thermal neutron capture (σ_{th}), resonance integral (I_o) and averaged fission neutron spectrum (FS), respectively. These are recently evaluated values [41].
[e] Values from [38].
[f] Either fixed on Dowex-50 or solvent extraction with HDEHP (di-(2-ethyl-hexyl)phosphoric acid).

flux in a reactor than that at a Ra/Be source, ^{32}P is produced in a reactor via this route in large quantities in nca form [25, 26]. The target material consists of purified ^{32}S powder, either pressed to a pellet or melted together, and placed in an Al capsule. The irradiation is done for several weeks at a fast neutron flux of about 2–3 × 10^{14} n cm^{-1} s^{-1}. Thereafter, the chemical processing is performed in two

ways: either ^{32}S is distilled over and ^{32}P is leached out with dilute HCl, or the target is melted and ^{32}P is leached out with H_2SO_4 and ethyl alcohol. Further purification of radiophosphorus is done through cation-exchange chromatography. The radionuclide ^{32}P is then finally achieved as $H_3{}^{32}PO_4$ in batch yields of about 100 GBq. It is commercially available.

^{89}Sr ($T_{½}$ = 50.5 d)

This radionuclide is partly produced via the $^{88}Sr(n,\gamma)^{89}Sr$ reaction. However, due to very low specific activity, the product $^{89}SrCl_2$ has been used only in palliative therapy of malignant metastases in the skeleton. For preparation of radiopharmaceuticals with high specific activity, a production route involving the neutron threshold reaction $^{89}Y(n,p)^{89}Sr$ has been developed [26]. The target material consists of Y_2O_3 powder pressed to a pellet, and placed in an Al capsule. The irradiation is done for several weeks at a fast neutron flux of $2–3 \times 10^{14}$ n cm^{-2} s^{-1}. Thereafter, the chemical processing starts by dissolving the irradiated target in HNO_3 and extracting the bulk of yttrium in tributylphosphate. The purification of ^{89}Sr is then done by incorporating several cation-exchange chromatographic steps. The finally purified product is then obtained as $^{89}SrCl_2$ in dilute HCl in a batch yield of about 20 GBq. Large quantities of this radionuclide are produced mainly at the reactor RIAR in Dimitrovgrad, Russia.

^{90}Y ($T_{½}$ = 2.7 d)

This radionuclide is easily produced via the $^{89}Y(n,\gamma)^{90}Y$ reaction even in a low-power reactor because the target is monoisotopic and the (n,γ) cross section with thermal neutrons is 1.28 b. However, for obtaining a product of high specific activity, the $^{90}Sr/^{90}Y$ generator system is used. The parent nuclide ^{90}Sr ($T_{½}$ = 28.9 a) is formed in the fission of ^{235}U with a high yield (5.77%) and is separated from the other fission products as $^{90}SrCl_2$ through a laborious procedure. The coproduced ^{89}Sr ($T_{½}$ = 50.5 d) is shorter lived and has a lower yield (4.69%), so it does not cause any serious problem in the preparation of the generator after a decay time of several months. The solution is fixed on a Dowex-50 cation-exchange chromatographic column and ^{90}Y is eluted with 0.003 M ethylenediaminetetraacetic acid for routine use. In another system, ^{90}Y is separated from the parent ^{90}Sr via batch extraction using di-(2-ethylhexyl)phosphoric acid [26]. Both generator systems are commercially available.

^{131}I ($T_{½}$ = 8.02 d)

This radionuclide is produced via two routes, namely fission of ^{235}U and the reaction sequence $^{130}Te(n,\gamma)^{131m,g}Te \xrightarrow{\beta^-} {}^{131}I$. Regarding the fission route, the irradiated $^{235}UAl_3$ pellet is first processed to extract ^{99}Mo (see above). Thereafter, radioiodine is separated by anion-exchange chromatography combined with a distillation step.

The radioiodine in the separated form exists as iodide. The method has been well established at the SAFARI reactor in Pretoria, South Africa, as well as at several other reactor sites. The yields achieved are sufficient for wide distribution.

Regarding the second route of production of ^{131}I, viz. the reaction sequence $^{130}\mathrm{Te}(\mathrm{n},\gamma)^{131\mathrm{m,g}}\mathrm{Te}\xrightarrow{\beta^-}{}^{131}\mathrm{I}$, the target material used is either pure Te metal or TeO_2. The cross sections for the formation of ^{131m}Te ($T_{½}$ = 30 h) and ^{131g}Te ($T_{½}$ = 25 min) with thermal neutrons are only 12 and 192 mb, respectively, calling for relatively long irradiations. The irradiation is therefore generally done for a few days at a neutron flux of ~10^{14} n cm^{-2} s^{-1}. The longer lived ^{131m}Te decays 77.8% by β^- emission directly to ^{131}I and 22.2% by IT to ^{131g}Te, which subsequently decays to ^{131}I. After a waiting time of about 2 days during which most of the ^{131m,g}Te has decayed to ^{131}I, the chemical processing is started. The metallic Te target is dissolved in an oxidizing mixture of chromic acid and H_2SO_4 and the radioiodine is distilled over and collected in a dilute solution of NaOH. The TeO_2 target, on the other hand, is subjected to the dry distillation process described earlier (cf. Chapter 4). The batch yield of ^{131}I obtained using the two target and processing systems is approximately the same. It is, however, lower than that via the fission route. In all three cases, the radioiodine obtained exists as iodide. In small reactor laboratories, the production of ^{131}I is mostly done via the activation of ^{130}Te to ^{131m,g}Te, followed by its decay to ^{131}I.

^{153}Sm ($T_{½}$ = 1.93 d)

This radionuclide is produced via the simple neutron capture reaction $^{152}\mathrm{Sm}(\mathrm{n},\gamma)^{153}\mathrm{Sm}$ [26]. The target isotope ^{152}Sm in ^{nat}Sm is only 26.75% but the cross section of the reaction is relatively high. So in many laboratories, Sm_2O_3 of natural isotopic composition is used as target. However, in order to increase the specific activity of the product and to avoid the longer lived radiocontaminants, like ^{145}Sm ($T_{½}$ = 340 d) and ^{151}Sm ($T_{½}$ = 93 a), >98% enriched $^{152}Sm_2O_3$ is utilized as a target. A few milligrams of the material is sealed in a quartz ampoule, which is placed in an Al capsule, and then irradiated in a medium flux reactor for several hours. At the end of the irradiation, the target material is taken up in ethylene diamine tetramethylene phosphoric acid (EDTMPA) dissolved in alkaline water. The solution is heated for about 1 h at 75 °C. Thereafter, it is used as a stock solution. The batch yield of ^{153}Sm is generally about 20 GBq and its specific activity about 18 GBq mg^{-1} of $^{152}Sm_2O_3$. For many studies, this specific activity is sufficient and, therefore, this radionuclide is finding increasing applications. But for some investigations, higher specific activity would be very desirable. Unfortunately, to date no method has been developed that would produce ^{153}Sm in nca form in sufficient quantity. The two hitherto investigated methods, namely $^{153}\mathrm{Eu}(\mathrm{n,p})^{153}\mathrm{Sm}$ and $^{140}\mathrm{Nd}(\alpha,\mathrm{n})^{153}\mathrm{Sm}$, deal only with nuclear reaction cross-section measurements, that is, no attempt at production has been reported.

^{177}Lu ($T_{½}$ = 6.65 d)

This radionuclide is produced either directly via the ^{176}Lu(n,γ)^{177}Lu reaction or indirectly via the route ^{176}Yb(n, γ)^{177}Yb $\xrightarrow{\beta^-}$ ^{177}Lu. Regarding the direct neutron capture process, both the thermal neutron cross section and the resonance integral are rather high, but since the abundance of ^{176}Lu in ^{nat}Lu is only 2.6%, often an enriched target (~43%) is used [25]. In a typical case, about 10 mg of $^{176}Lu_2O_3$ is sealed in a quartz tube and irradiated at a neutron flux of ~ 1×10^{14} n cm^{-2} s^{-1} for a few days. After the irradiation the target is dissolved in HCl. The final product $^{177}LuCl_3$ is obtained in a high batch yield. There are, however, two major drawbacks of the method: first, the specific activity of the product is limited to about 1600 GBq mg^{-1} of Lu after a 4 d irradiation in a relatively high flux reactor and second, the longer lived ^{177m}Lu ($T_{½}$ = 160.4 d), also formed during the irradiation, is present in a small amount (0.012%).

The second route of production involving the activation of ^{176}Yb to ^{177}Yb ($T_{½}$ = 1.9 h) followed by its decay leads to much lower batch yield of ^{177}Lu. This is due to two reasons: (a) abundance of only 12.7% of the target nuclide ^{176}Yb in natural Yb, (b) rather low neutron capture cross section and resonance integral (see Table 5.5). In many cases, therefore, about 96% enriched $^{176}Yb_2O_3$ is used as a target material. In a typical run, about 10 mg of the material is sealed in a quartz ampoule and irradiated in a nuclear reactor for a few days. The chemical processing of the irradiated target is started by its dissolution in HCl. Thereafter, nca ^{177}Lu is separated from the bulk of Yb by ion-exchange chromatography. The separation is typical of those encountered in nuclear reaction studies, where the target material is bulky and the reaction product is at nca level. However, because of the intended medical use, the purity criteria are much more stringent than in nuclear reaction studies. As a result of several recent studies, $^{177}LuCl_3$ of specific activity approaching about 3000 GBq mg^{-1} of Lu has been achieved [25]. This is by a factor of about 2.0 higher than that via the direct route. A further advantage of the indirect route of ^{177}Lu production is the much lower level of the ^{177m}Lu impurity (<10^{-4}%). The total yield of ^{177}Lu via the indirect route is, however, much lower.

It should be mentioned that production of ^{177}Lu through charged-particle induced reactions, for example, Ta(p,spall), Hf(p,x) and ^{176}Yb(d,n), has also been investigated. However, due to low cross sections and high impurity levels involved, none of those reactions was found to be of practical value.

^{188}Re ($T_{½}$ = 17.0 h)

This radionuclide can be produced directly via the ^{187}Re(n,γ)^{188}Re reaction or via the ^{188}W/^{188}Re generator system. Originally, the direct production route was used. However, due to the very low specific activity of the product, combined with the development of the convenient ^{188}W/^{188}Re generator system, the direct production route is now rarely used. The indirect route, however, is not easy to follow in

a normal reactor because it is based on a two-step neutron capture process. In the first step, the reaction $^{186}W(n,\gamma)^{187}W$ occurs. The product ^{187}W is radioactive and decays with a half-life of 23.7 h. It has, however, a rather high neutron capture cross section as well, so that there is a competition between radioactive decay of ^{187}W and the $^{187}W(n,\gamma)$ ^{188}W reaction, the latter leading to the formation of ^{188}W ($T_{1/2}$ = 69.8 d). As expected the second neutron capture process is favoured in a relatively high flux reactor. For production of ^{188}W, a metallic or oxide tungsten target is used. Typical irradiations at neutron fluxes between 5×10^{14} and 2×10^{15} n cm^{-2} s^{-1} are done for several weeks. The chemical processing of the irradiated target involves dissolution in hot 1 M NaOH in the presence of H_2O_2 followed by several purification steps to obtain pure ^{188}W. Presently large quantities of ^{188}W are produced mostly at the Oak Ridge National Laboratory, followed by smaller amounts at the University of Missouri. The method is also under development at Dimitrovgrad.

For preparation of the $^{188}W/^{188}Re$ generator, the purified ^{188}W is generally loaded on an Al_2O_3 column and, similar to the $^{99}Mo/^{99m}Tc$ generator, elution of the ^{188}Re is done with saline. A few other types of generators have also been reported.

Other β^- Emitters

In addition to the above discussed standard β^--emitting therapeutic radionuclides, there are many others which have also found some application or which are potentially useful. Among them are ^{47}Sc, ^{67}Cu, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{114m}In, ^{137}Cs, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{175}Yb, ^{186}Re and ^{192}Ir. Furthermore, the X-ray emitter ^{131}Cs and the Auger electron emitters ^{117m}Sn, ^{193m}Pt and ^{195m}Pt are also interesting therapeutic radionuclides. Among those radionuclides, ^{192}Ir ($T_{1/2}$ = 73.8 d) and ^{137}Cs ($T_{1/2}$ = 30.2 a) find some application in brachytherapy or external irradiation of the retina, respectively. They are produced via the (n,γ) and the (n,fission) process, respectively. Some of the other radionuclides have either already been produced using nuclear reactors, or their production methods are in development. In particular, the radiolanthanides are of considerable interest [157]. For example, the radionuclides ^{165}Dy ($T_{1/2}$ = 2.3 h), ^{166}Ho ($T_{1/2}$ = 1.1 d), ^{169}Er ($T_{1/2}$ = 9.4 d) and ^{175}Yb ($T_{1/2}$ = 4.2 d) are occasionally used in palliative therapy of inflammatory joint diseases. Similar to ^{153}Sm they are all produced via the (n,γ) reaction. In addition, ^{166}Ho is also obtained via the $^{166}Dy/^{166}Ho$ generator system, whereby the parent ^{166}Dy ($T_{1/2}$ = 3.4 d) is produced through the double neutron capture reaction $^{164}Dy(n,\gamma)^{165}Dy(n,\gamma)^{166}Dy$, similar to the case of ^{188}W described above. On the other hand, in several cases, new demands on purity and specific activity have led to stronger efforts to develop more efficient production methods. Some of those efforts are given due consideration in Chapter 6 where newer developments are treated in detail.

5.5 Standard α-Particle Emitters for Targeted Therapy

The highly ionizing property of α-particles was recognized soon after the discovery of natural radioactivity and in that early phase it was rather extensively used in external local therapy of skin diseases on empirical basis, that is, without properly understanding the biological effects. Today, α-radiation is used internally in the form of "*targeted therapy*," which calls upon great skills and expertise in the choice of the α-particle emitter and in the nature of the designed targeted molecular carrier [158]. The therapeutic value of α-particles is based on their short-range and high linear energy transfer (LET), amounting to about 100 keV μm^{-1}, compared to a value of about 0.2 keV μm^{-1} for a high-energy β^- particle (see also Appendix IV). Since the relative biological effectiveness of radiation is maximum at LET values of about 100 keV μm^{-1} [158], internal radionuclide therapy using α-particles is of great interest.

Although approximately 100 radionuclides are known to decay by α-particle emission, only a few have appropriate properties for internal radionuclide therapy in humans [159]. The four more commonly used ones are ^{211}At, ^{213}Bi, ^{223}Ra and ^{225}Ac. Their production routes are discussed below.

^{211}At ($T_{½}$ = 7.2 h)

This radionuclide has been under consideration for more than 40 years. It decays by direct α-particle emission (42%) to ^{207}Bi or by EC (58%) to ^{211}Po ($T_{1/2}$=0.5 s), followed by α-emission. Thus, each decay of ^{211}At is associated with the emission of an α-particle. Astatine is a halogen and the expectation had been that several of the radioiodination methods could be adapted to ^{211}At. However, astatine also exhibits metallic character under certain conditions. To date astatine has been used to attach to antibodies, proteins and inorganic colloids. The main problem, however, is the stability of the compound under physiological conditions. Nonetheless, considerable progress has been achieved in α-therapy using ^{211}At-labelled compounds.

For the production of ^{211}At several nuclear processes have been used, involving either a direct route or an indirect route via the decay of the parent ^{211}Rn (for an early review see Appendix II, and for a recent review cf. [160]). The parent ^{211}Rn ($T_{½}$ = 14.6 h) is obtained in a small quantity either through the spallation of ^{232}Th or via the ^{209}Bi(^{7}Li,5n)^{211}Rn reaction. In recent years, some new attempts have been successful in producing ^{211}At via the indirect route in small quantities for preclinical research [161]. Nonetheless, the method of choice remains the direct production reaction ^{209}Bi(α,2n)^{211}At. The excitation function is known very well [41]. For production, the energy of the α-particles must be kept below 29 MeV to avoid the formation of ^{210}At ($T_{½}$ = 8.1 h), which decays to longer lived α-particle emitting radionuclide ^{210}Po ($T_{½}$ = 138.0 d) and causes high extra radiation dose. For the optimum energy range of $E_α$ = 28 → 20 MeV, the calculated

yield of ^{211}At amounts to 25.3 MBq μA h^{-1}, without any contamination from ^{210}At. The target for irradiation generally consists of a thin layer of Bi (melted, pressed or vacuum evaporated) on an Al backing. High current irradiations in internal target systems using slanting beams have been reported [162, 163]. In a 4 h irradiation at 55 μA beam current, a batch yield of up to 7 GBq ^{211}At was reported [162]. The standard method for removing ^{211}At from the irradiated target is by dry distillation at 650 °C in an Ar stream (cf. Chapter 4). The ^{211}At removed from the distillation apparatus is trapped at −77 °C. For subsequent radiosynthesis work, the trapped astatine is recovered with a small volume of organic solvent. Very recently an automated flow system has been developed [164] which incorporates in-line acid dissolution of irradiated bismuth metal for use in the isolation of ^{211}At. In irradiations of Bi targets (of masses about 4.5 g) with 40 μA α-particle beams for about 50 min, the batch yield of ^{211}At amounted to about 1 GBq [164]. Thus, sufficient quantities of this radionuclide could be made available for patient studies. However, due to the short half-life of the radionuclide, formation of a network of cyclotrons delivering 30 MeV α-particles is being attempted both in Europe and in the USA.

^{213}Bi ($T_{½}$ = 45.6 min)

This radionuclide decays only 2.2% via α-particle emission directly to ^{209}Tl and 97.8% through β^- decay to ^{213}Po ($T_{½}$ = 3.7 μs), which decays further 100% by α-particle emission to ^{209}Pb ($T_{½}$ = 3.2 h). Thus, each decay of ^{213}Bi is associated with the emission of an α-particle. This relatively short-lived α-particle emitter is obtained from a generator system loaded with the parent activity ^{225}Ac ($T_{½}$ = 10.0 d). The radionuclide ^{225}Ac itself is difficult to produce (see below) and the question existed whether a short-lived α-particle emitter would be effective enough as a therapeutic agent. Some recent studies on prostate-specific membrane antigen(PSMA)- monoclonal antibody labelled with ^{213}Bi have, however, led to the convincing result [165] that some β^--resistant tumours can be effectively handled using this radionuclide, if multiple applications are carried out. Further development and optimisation work on the generator system to ensure a regular and reliable supply of ^{213}Bi thus appears worthwhile.

^{223}Ra ($T_{½}$ = 11.4 d)

This radionuclide is a 100% α-particle emitter. Its importance has grown in recent years and it has now been approved for use in the form of $^{223}RaCl_2$ as a drug in many jurisdictions, especially for treatment of blood cancer. It was first obtained via the chain $^{226}\mathrm{Ra}\,(\mathrm{n},\gamma)^{227}\mathrm{Ra}\,(42.2\,\mathrm{min}) \xrightarrow{\beta^-} {}^{227}\mathrm{Ac}\,(21.8\,\mathrm{a}) \xrightarrow{\beta^-} {}^{223}\mathrm{Ra}$. The parent activity ^{227}Ac is available in a certain limited quantity and ^{223}Ra is periodically removed from it. In view of the increasing significance of this radionuclide, more ^{227}Ac needs

to be produced. A potentially interesting production route involving the irradiation of ^{232}Th with intermediate energy protons is being developed, especially at Los Alamos. This route is discussed in the next chapter together with work on other novel radionuclides.

^{225}Ac ($T_{½}$ = 10.0 d)

This radionuclide decays via the series:

$$^{225}\mathrm{Ac} \xrightarrow{\alpha} {}^{221}\mathrm{Fr}\,(4.9\,\mathrm{min}) \xrightarrow{\alpha} {}^{217}\mathrm{At}\,(32\,\mathrm{ms}) \xrightarrow{\alpha} {}^{213}\mathrm{Bi}\,(45.6\,\mathrm{min}) \xrightarrow{\beta^-}$$
$$^{213}\mathrm{Po}\,(3.7\,\mu\mathrm{s}) \xrightarrow{\beta^-} {}^{209}\mathrm{Pb}\,(3.2\,\mathrm{h}) \xrightarrow{\beta^-} {}^{209}\mathrm{Bi}$$

Thus each decay of ^{225}Ac results in the production of four α-particles, making it an extremely potent therapeutic source. On the other hand, the decay chain products ^{221}Fr and ^{213}Bi have measureable half-lives, raising some concern that the release of those radionuclides may result in excessive toxicity to normal organs. Today, this radionuclide is used directly but also as a generator parent of ^{213}Bi for therapeutic application (see above).

Extensive efforts have been devoted to production of ^{225}Ac. Its separation from nuclear waste (^{229}Th) has been optimised [166], and generators are now commercially available. However, the total amount of ^{225}Ac activity available per year is limited to about 75 GBq. In view of the increasing demand of this radionuclide, two cyclotron production processes, namely ^{226}Ra(p,2n)^{225}Ac and ^{232}Th(p,spall)^{225}Ac, are being developed The cross-section data of those reactions have been described in Chapter 2 (Section 2.5.5). Since further extensive work is continuing, those two cyclotron production routes are discussed in more detail in Chapter 6, which deals with the development of novel radionuclides.

5.6 Concluding Remarks

In this chapter, the basic technology of production of standard medical radionuclides has been described. The methodology is generally well established and the radionuclides are commonly available for routine patient care studies, involving both diagnosis and therapy. Occasionally, some improvement in a production method may be needed to meet newer quality requirements. The major thrust regarding each commonly available radionuclide, however, is towards developing newer radiopharmaceuticals for preclinical or clinical research. The production of the radionuclide then becomes the realm of the industry.

In medical research it is also often realized that the standard radionuclides described in this chapter are not sufficient for many investigations. This calls upon

the development of novel radionuclides rather than radiopharmaceuticals. In those cases, more attention is paid to nuclear, radiochemical and technological aspects of the production process under consideration. The guiding principle in all those studies is to develop a method that would allow the production of the radionuclide in a suitable form and in sufficient quantity for a specific medical application. Thus, a blend of fundamental research and technological work is involved.

6 Development of Novel Medical Radionuclides

Besides routine production of standard medical radionuclides for patient care studies (as discussed in Chapter 5), in recent years considerable work has been done towards development of research-oriented novel radionuclides. The present emphasis is on two types of radionuclides, namely, non-standard positron emitters for positron emission tomography (PET) and highly ionizing low-range radiation emitters for internal radiotherapy. Some attention is also being devoted to γ-emitting radionuclides for potential use in single-photon emission computed tomography (SPECT). The general scientific background to development work related to radionuclide production has been provided in Chapters 2–4. In this chapter, some of the technical details of production of several novel radionuclides are given.

6.1 Non-standard Positron Emitters

6.1.1 General

With the growing significance of PET in diagnostic nuclear medicine, the need for innovative, non-standard positron emitters has been increasing, especially for studying slow functional processes and for quantification of targeted therapy. In particular, many non-standard positron emitters are finding application in *theranostics*. This concept involves the simultaneous use of a positron emitter and a therapeutic radionuclide of the same element while carrying out investigations on a particular person. Thus, the chemistry during diagnosis and therapy remains unchanged. This type of treatment is termed as *personalised medicine*.

As mentioned in Chapter 2, the status of *decay data* of non-standard positron emitters is not as good as of standard positron emitters. The distinctive decay features of non-standard positron emitters (in comparison to standard positron emitters) are: (a) relatively longer half-lives, (b) rather high positron endpoint energies, (c) generally low positron intensities and (d) associated γ-rays. These features affect the resolution of scans and call upon the development of some special algorithms in the analysis of images. Nonetheless, to date about 30 non-standard positron emitters have been developed for medical applications. The various aspects of development work have been elucidated (see Appendix V). An updated review discusses some more recent work [167]. Table 6.1. gives a summary of all non-standard positron emitters for which some sort of biological application has been demonstrated. Among the *decay data* listed are half-lives, positron endpoint energies, positron emission intensities and most intense γ-rays (taken mostly from [23, 24]). The half-lives are well known, but inconsistencies are observed in the intensities of the emitted positrons. Although in a few cases new measurements have been carried out, especially at the

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Table 6.1: Production methods of some useful and potentially useful non-standard positron emitters.*

Positron emitter	$T_{½}$	$E_{\beta+}$[b] (keV)	$I_{\beta+}$[c] (%)	Major γ-ray energy in keV(%)	Nuclear reaction[a]	Energy range (MeV)	Thick target yield[g] (MBq μAh^{-1})	Target material, enrichment (%)	Typical batch yield (MBq)	References to production work
Low-energy range										
^{34m}Cl	32.2 min	4500	54.0	146 (40.5)	^{36}Ar(d,α)[e]	8 → 3	252	^{36}Ar gas (99.99)	700	[171]
^{38}K	7.6 min	2724	99.4	2168 (99.9)	^{38}Ar(p,n)[e]	16 → 12	777	^{38}Ar gas (95.7)	200	[172]
^{44}Sc	3.9 h	1474	94.3	1157 (99.9)	^{44}Ca(p,n)[e]	18 → 6	2.6×10^3	$^{44}CaCO_3$ (94.5)	2.5×10^3	[219, 220]
^{45}Ti	3.1 h	1040	85.7	719 (0.12)	^{45}Sc(p,n)	14.5 → 5	433	Sc foil	2.1×10^3	[224–226]
^{51}Mn	46.2 min	2185	96.9	749 (0.26)	^{50}Cr(d,n)[e]	13 → 8	900	$Al_4{}^{50}CrCl_3$ (94.7)	107	[176]
^{52}Mn	5.6 d	575	29.6	1434 (100)	^{nat}Cr(p,x)	17 → 8	14	Cr sheet, pellet or electroplated	150	[54, 177–180]
^{55}Co	17.5 h	1498	76.0	931 (75) 477 (20)	^{54}Fe(d,n)[e] ^{58}Ni(p,α)[e]	10 → 5 15 → 7	30 14	$^{54}Fe_2O_3$ (91.6) ^{58}Ni electroplated (99.9)	240 160	[181] [109]

^{61}Cu	3.3 h	1215	62[f]	283 (12.5)	^{61}Ni(p,n)[e] ^{64}Zn(p,α)[e]	15 → 7 18 → 11	1418 288	^{61}Ni electroplated (88.8) ^{64}Zn electroplated (99.3)	5×10^3 1×10^3	[65, 182] [228]
^{64}Cu	12.7 h	653	17.8[d]	1346 (0.54)	^{64}Ni(p,n)[e]	12 → 8	304	^{64}Ni electroplated (95.0)	40×10^3	[65, 182–191]
^{66}Ga	9.5 h	4153	56[f]	1039 (38)	^{66}Zn(p,n)[e]	15 → 7	700	^{66}Zn electroplated (99.3)	3×10^3	[237]
^{75}Br	1.6 h	2008	73.0	286 (92)	^{78}Kr(p,α)[e]	17 → 11	70	^{78}Kr gas (99.4)	< 150	[238, 246]
^{76}Br	16.2 h	3941	58.2	559 (74)	^{76}Se(p,n)[e]	15 → 7	402	$Cu_2{}^{76}Se$ (96.5)	~ 300	[235]
^{82m}Rb	6.5 h	899	21[f]	776 (84.5)	^{82}Kr(p,n)[e]	14.5 → 10	370	^{82}Kr gas (72.9)	400	[120]
^{86}Y	14.7 h	3153	33[f]	1077 (82.5)	^{86}Sr(p,n)[e]	14 → 7	371	$^{86}SrCO_3$ pellet (96.5)	3×10^3	[138, 139, 141, 195–199]
^{89}Zr	3.27 d	897	22.3	909 (100)	^{89}Y(p,n)	14 → 9	58	Y metal	2×10^3	[205–207]
^{90}Nb	14.6 h	1500	51.2	1129 (92.7)	^{90}Zr(p,n)[e]	15 → 8	423	^{nat}Zr metal	202	[239]
^{94m}Tc	52.5 min	2470	72.0	871 (94.2)	^{94}Mo(p,n)[e]	13 → 7	2×10^3	$^{94}MoO_3$ (94.0)	10×10^3	[101, 135, 208]
^{120g}I	1.3 h	4593	56[f]	560 (73)	^{120}Te(p,n)[e]	15 → 9	2×10^3	$^{120}TeO_2$ (99.9)	700	[54, 112]

(continued)

Table 6.1 (continued)

Positron emitter	$T_{½}$	$E_{\beta+}$[b] (keV)	$I_{\beta+}$[c] (%)	Major γ-ray energy in keV(%)	Nuclear reaction[a]	Energy range (MeV)	Thick target yield[g] (MBq μAh^{-1})	Target material, enrichment (%)	Typical batch yield (MBq)	References to production work
^{124}I	4.18 d	2137	22.0	603 (61)	^{124}Te(p,n)[e]	12 → 8	16	$^{124}TeO_2$ (99.8)	500	[112, 209–213]
Intermediate-energy range										
^{30}P	2.5 min	3245	99.9	2235 (0.06)	^{27}Al(α,n)	28 → 10	ca. 1000	Al sheet	1×10^3	[173, 174]
^{34m}Cl	32.2 min	4500	54.0	146 (40.5)	^{32}S(α,d)	50 → 20	1608	S molten	500	[170]
^{38}K	7.6 min	2724	99.4	2168 (99.9)	^{35}Cl(α,n) ^{40}Ar(p,3n)	22 → 7 39 → 23	ca. 400 550	NaCl pellet ^{nat}Ar gas	600 610	[175] [244]
^{44}Sc	3.9 h	1474	94.3	1157 (99.9)	^{44}Ca(d,2n)[e45] Sc(p,2n)^{44}Ti[h]	25 → 10 35 → 15	2.5×10^3 0.0043[i]	$^{44}CaCO_3$ (94.5) Generator	8 185 (daughter)	[221, 222] [215, 218]
^{52}Fe	8.3 h	806	55.5	169 (99.2)	^{55}Mn(p,4n) ^{nat}Cr(α,xn) ^{nat}Cr(^{3}He,xn) ^{nat}Ni(p,x)	100 → 60 30 → 20 36 → 17 70 → 60	22 0.11 1.3 21	Mn sintered pellet Cr electroplated Cr metal Ni sheet; Ni tablet	1.5×10^3 400 8 3×10^3	[242] [240] [240, 241] [242, 243]

^{61}Cu	3.4 h	1215	62[f]	283 (12.5)	^{59}Co(α,2n)	33 → 23	185	Co metal	1.5×10^3	[229, 230]
^{62}Cu	9.7 min	2926	97.4	1173 (0.34)	^{nat}Cu (p,xn)^{62}Zn	30 → 20	176[i]	Generator	700 (daughter)	[248, 249]
^{64}Cu	12.7 h	653	17.8[d]	1346 (0.54)	^{68}Zn(p,αn)[e]	30 → 20	116	^{68}Zn electroplated (99.7)	< 200	[193]
					^{64}Zn(d,2p)[e]	20 → 10	27	^{64}Zn electroplated (99.3)	< 200	[192]
^{72}As	1.08 d	3334	87.8	834 (79.5)	^{75}As(p,4n) ^{72}Se[h]	45 → 35	8	in development		[71, 250]
					^{nat}Br(p,x)^{72}Se[h]	100 → 70	3	in development		[251]
^{73}Se	7.1 h	1651	65.4	361 (97)	^{75}As(p,3n)	40 → 30	1.4 × 10^3	As_2O_3; Cu_3As	6×10^3	[71, 231]
					^{70}Ge(α,n)[e]	28 → 13	126	$Cu_3{}^{70}Ge$ (96.7)	2×10^3	[134]
^{75}Br	1.6 h	2008	73.0	286 (92)	^{75}As(^{3}He,3n)	36 → 25	278	Cu_3As	3×10^3	[108]
					^{76}Se(p,2n)[e]	24 → 11	1.2 × 10^3	^{76}Se metal (96.5)	6×10^3	[111]
^{76}Br	16.2 h	3941	58.2	559 (74)	^{75}As(^{3}He,2n)	18 → 10	11	Cu_3As	600	[108, 234]
^{77}Kr	1.2 h	2041	84.0	130 (80)	^{77}Se(^{3}He,3n)[e]	36 → 15	425	^{77}Se metal (94.4)	2×10^3	[110]
^{81}Rb	4.6 h	1026	27[f]	190 (64.3)	^{82}Kr(p,2n)[e]	27 → 19	1.8 × 10^3	^{82}Kr gas (72.9)	400	[255]
^{83}Sr	1.35 d	1254	26[f]	763 (30)	^{85}Rb(p,3n)[e]	37 → 30	160	^{85}RbCl (99.4)	< 100	[247]
^{86}Y	14.7 h	3153	33[f]	1077 (82.5)	^{88}Sr(p,3n)[e]	43 → 33	1.0 × 10^3	$SrCl_2$ pellet	4×10^3	[252]

(continued)

Table 6.1 (continued)

Positron emitter	$T_{½}$	$E_{\beta+}$[b] (keV)	$I_{\beta+}$[c] (%)	Major γ-ray energy in keV(%)	Nuclear reaction[a]	Energy range (MeV)	Thick target yield[g] (MBq μAh^{-1})	Target material, enrichment (%)	Typical batch yield (MBq)	References to production work
^{140}Pr	3.4 min	2366	50.8	1596 (0.5)	^{141}Pr(p,2n)^{140}Nd[h]	30 → 15	210[i]	In vivo generator	~200 (daughter)	[253]
^{152}Tb	17.5 h	2500	18[f]	344 (57)	^{nat}Nd(^{12}C,xn) ^{nat}Ta(p,spall)	110 → 80 ~ 1000	~10[i] ~60[i]	Nd metal Ta metal, online mass separation	~20 700	[98] [99, 245]

[*] Adapted partly from Qaim [36], with permission from Elsevier, and extended for production data.

[a] The references to all original papers on nuclear reaction cross-section data are to be found in Appendix V and in a recent review article [36]. Here only references to the production data are given.

[b] Endpoint energy of the positrons.

[c] This is the intensity of positrons in %; the rest is EC, unless otherwise stated.

[d] For ^{64}Cu the intensities in % are: β^+ (17.8), EC (43.8); β^- (38.4).

[e] Using highly enriched isotope as target material.

[f] $I_{\beta+}$ value has rather large uncertainty.

[g] Calculated from the excitation function (unless otherwise stated) for an irradiation time of 1 h.

[h] Generator parent.

[i] Yield of parent.

[j] Experimental yield (MBq μAh^{-1}).

Forschungszentrum Jülich, and improved data on the positron emission intensities of ^{45}Ti, ^{64}Cu, ^{76}Br, ^{120}I and ^{124}I have been made available [37, 168, 169], for many other positron emitters further measurements are needed. For example, some uncertainties exist in the positron branchings of the radionuclides ^{61}Cu, ^{66}Ga, ^{81}Rb, ^{82m}Rb, ^{83}Sr, ^{86}Y, ^{120g}I and ^{152}Tb.

The investigated *production routes* of non-standard positron emitters are also listed in Table 6.1., together with the optimum energy ranges and the thick target yields calculated from the excitation functions. Recently, the status of the production data was critically reviewed and the updated references to papers dealing with cross sections were given [36]. Most of the measurements using enriched target isotopes were done at the Forschungszentrum Jülich. A large number of radionuclides can be produced using a small-sized (Level III) two-particle cyclotron (with E_p < 20 MeV; E_d < 10 MeV). The common route of production is the low-energy (p,n) reaction on the respective enriched target isotope, and the radionuclides ^{44g}Sc, ^{45}Ti, ^{52g}Mn, ^{61}Cu, ^{64}Cu, ^{66}Ga, ^{76}Br, ^{82m}Rb, ^{86}Y, ^{89}Zr, ^{94m}Tc, ^{120}I and ^{124}I have been produced on a clinical scale via this route, mostly using a solid target but, in recent years, also a solution target (cf. sections 3.3.2 and 3.3.3). In a few cases other low-energy reactions, such as (d,n), (d,α) and (p,α), especially for the production of sufficient quantities of ^{34m}Cl, ^{51}Mn and ^{55}Co, have also been employed. On the other hand, many useful or potentially useful positron emitters can be produced only using intermediate energy reactions at energies above 30 MeV, in a few cases above 50 MeV. For example, the production of the radionuclides ^{52}Fe, ^{57}Ni, ^{73}Se, ^{77}Kr and ^{83}Sr can be done only via (p,xn) reactions, demanding a high-intensity cyclotron or accelerator, which delivers protons of energies up to about 70 MeV (in the case of ^{52}Fe up to 100 MeV). Similarly the parents of a few novel generator systems, for example, ^{44}Ti (60.4 a)/^{44}Sc (3.9 h), ^{72}Se (8.5 d)/^{72}As (26.0 h) and ^{140}Nd (3.4 d)/^{140}Pr (3.4 min), can be produced only using intermediate energy protons. On the other hand, in a few special cases, besides protons, ^{3}He- and α-particles of intermediate energy may also be advantageously used for production purposes, for example, ^{75}Br and ^{76}Br via (^{3}He,xn)-reactions and ^{30}P, ^{38}K, ^{61}Cu and ^{73}Se via (α,xn)-reactions on relevant targets. In all cases where at least a small-scale production has been reported, the targets used and the batch yields achieved are given in Table 6.1. In the case of an isotopically enriched target, the recovery of the enriched material is always incorporated in the separation process. The references given in Table 6 1. specifically deal with the production aspects [170–255].

6.1.2 Established Non-standard Positron Emitters

Of all the non-standard positron emitters studied, six of them, namely, ^{52g}Mn, ^{64}Cu, ^{86}Y, ^{89}Zr, ^{94m}Tc and ^{124}I, are finding broader interest and their clinical-scale production via the (p,n) reaction has been developed in several laboratories. Their production methods are discussed below.

^{52g}Mn (T½ = 5.6 d)

This radionuclide emits low-energy positrons. The positron intensity is only 29.6% and the half-life is relatively long. Nonetheless, it is suitable for PET imaging. For its production several reactions were investigated (for early review see Appendix I), out of which the ^{52}Cr(p,n) reaction was found to be the most suitable and has been used in recent years for production purposes. The target for irradiation consists of either enriched ^{52}Cr or ^{nat}Cr electroplated on a Au backing or simply a high-purity chromium disk. Irradiation is generally done for a few hours using a slanting beam of protons of up to 20 μA [cf. 54]. For the separation of nca ^{52g}Mn from the bulk of chromium, several methods have been reported, based mainly on coprecipitation and anion-exchange chromatography. Some improvements have been introduced in recent years [54, 177–180]. In a novel method [178], the chemical processing starts by dissolution of the target in HCl at 70 °C, followed by a vigorous treatment of the solution to remove the chloride ion and to render the solution in 0.1 M H_2SO_4. This solution is then loaded onto a cation-exchanger Dowex 50W×8, preconditioned with 0.1 M H_2SO_4. On elution with 0.1 M H_2SO_4, chromium is quantitatively removed. Thereafter the column is loaded with a solution of 0.01 M hydrazine sulfate to reduce radiomanganese to Mn^{2+}, which is then finally eluted with a solution of 0.067 M ammonium citrate (pH = 7.3). The separated ^{52g}Mn was found to be of high radionuclidic, radiochemical and chemical purity. The batch yield of ^{52g}Mn achieved was ca. 150 MBq.

The radionuclide ^{52g}Mn is of great importance in combining PET and MRI (magnetic resonance imaging). In view of its increasing significance in authentic radiolabelling of new manganese contrast agents for MRI, intensified efforts are presently being devoted to produce this radionuclide in larger quantities.

^{64}Cu (T½ = 12.7 h)

This radionuclide emits low-energy positrons, has no disturbing γ-ray, has a suitable half-life and forms interesting stable coordination complexes. It is thus very suitable for studying slow functional processes. However, the positron branching is only 17.8%. Thus, much higher radioactivity has to be injected to achieve a coincidence rate similar to that of ^{18}F-radiopharmaceuticals. In addition, the remaining 82.2% decay branching (β^-, EC) induces a non-negligible radiation dose. On the other hand, due to its relatively low β^+ energy, the resolution of PET scans with ^{64}Cu is almost as good as with ^{18}F. Because of these reasons, ^{64}Cu is used in radioimmunotherapy. It also allows a combination of PET with radiotherapy, that is, the application of the theranostic approach (in combination with the therapeutic radionuclide ^{67}Cu).

Based on a critical analysis of the published nuclear reaction cross sections, a comparison of the various production routes of ^{64}Cu was presented [64]. A summary is given in Table 6.2. Of all the investigated processes, the ^{64}Ni(p,n)^{64}Cu reaction

Table 6.2: Comparison of production routes of $^{64}Cu^{*}$.

Nuclear process	Optimum energy range (MeV)	Thick target yield [d] (MBq μAh^{-1})
$^{64}Ni(p,n)^{64}Cu$[a]	12 → 8	304
$^{64}Ni(d,2n)^{64}Cu$[a]	17 → 11	430
$^{68}Zn(p,\alpha n)^{64}Cu$[a]	30 → 21[b]	116
$^{66}Zn(p,2pn)^{64}Cu$[a]	52 → 37	316
$^{64}Zn(d,2p)^{64}Cu$[a]	20 → 10	27
$^{66}Zn(d,\alpha)^{64}Cu$[a]	13 → 5	13.8
$^{nat}Zn(d,x)^{64}Cu$	25 → 10[c]	57.0

[*] After Aslam et al. [64], with courtesy of De Gruyter.
[a] Using highly enriched target material; low enrichment will lead to impurities.
[b] Below the threshold of the ^{67}Cu impurity via the $^{68}Zn(p,2p)^{67}Cu$ reaction.
[c] Below thresholds of ^{61}Cu and ^{67}Cu impurities via the $^{64}Zn(d,\alpha n)^{61}Cu$ and $^{68}Zn(d,2pn)^{67}Cu$ reactions, respectively.
[d] Calculated from the excitation function, assuming 100 % enrichment of the target isotope (unless mentioned otherwise) for an irradiation time of 1 h.

was found to be the best. It gives the product in high yield and with high specific activity. Although it involves the use of rather expensive highly enriched target material, generally electroplated on a Au backing, the technology has been fully developed [65, 182–191] utilizing this route for the production of ^{64}Cu over the energy range of E_p = 12 → 8 MeV. Batch yields of about 40 GBq ^{64}Cu are achieved and the enriched target material ^{64}Ni is efficiently recovered. The separation of ^{64}Cu is generally done via anion-exchange chromatography and the quality of the product is acceptable for subsequent radiopharmaceutical production. Due to the increasing demand for this radionuclide, a commercialization of the process is now being pursued. On the other hand, small quantities of ^{64}Cu for local use are produced using the same nuclear reaction and a solution target at a medical cyclotron. Furthermore, tracer amounts of ^{64}Cu have also been produced using the nuclear processes $^{64}Zn(d,2p)^{64}Cu$ [192] and $^{68}Zn(p,\alpha n)^{64}Cu$ [193]. In both cases, modified forms of ion-exchange chromatography were used for the separation of ^{64}Cu.

^{86}Y ($T_{½}$ = 14.7 h)

This radionuclide decays via electron capture and positron emission, followed by emission of more than 12 γ-rays. There are six positron groups with varying endpoint energies (maximum = 3153 keV) and intensities, the total β^+ emission intensity amounting to about 33%. In view of the rather high positron energy and presence of several γ-rays in the vicinity of the annihilation radiation, it was expected that

this radionuclide would require considerable effort to make its use in PET investigations. Nevertheless it was developed [68, 138] and administered to a patient [194] together with the therapeutic radionuclide ^{90}Y ($T_{½}$ = 2.7 d). A following PET measurement [194] led to an exact estimation of the dose from the ^{90}Y-labelled compound in terms of mGy per MBq of ^{90}Y. This investigation is regarded today as the *initiation of the theranostic approach in nuclear medicine*. The subsequent historical development has been described in a recent article [67].

A critical evaluation of the data [66] for the investigated nuclear reactions showed that for the production of ^{86}Y, the ^{86}Sr(p,n)^{86}Y reaction on a highly enriched target covering the energy range E_p = 14 → 7 MeV is most suitable (see Section 2.5.3). The production methodology is established [138, 139, 141, 195–199]. Very recently some preliminary results on a new route, namely, $^{89}\mathrm{Y}(\mathrm{p},4\mathrm{n})^{86}\mathrm{Zr} \overset{\mathrm{EC},\beta^+}{\rightarrow} {}^{86}\mathrm{Y}$, have been reported [200], but further investigations are needed to exhibit its suitability for production of ^{86}Y.

In contrast to a relatively small number of nuclear data measurements and use of only one target material ($^{86}SrCO_3$: 96–97 % enriched) for irradiations, the efforts devoted to chemical separation of radioyttrium have been extensive [138, 139, 141, 195–199, 201–203] and six methods have been investigated. They involve precipitation and ion-exchange chromatography, electrolysis, single column chromatography, multiple column chromatography, solvent extraction and precipitation of the target element. A brief overview is given in Table 6.3. and a detailed discussion elsewhere [67]. Out of those processes, the method involving

Table 6.3: Overview of separation methods of ^{86}Y from a $SrCO_3$ target used in real production runs via the ^{86}Sr(p,n)^{86}Y reaction.

Method	Efficiency of chemical separation(%)	Typical production batch yield (GBq)	Volume of final solution	Sr chemical impurity (ng mL^{-1})	References
Coprecipitation and ion-exchange	90	1.3–3.5	150 µL	2.6	[138, 139]
Electrolysis	90	1.2	250 µL	100–700	[141, 196]
Single-column cation exchange	90	0.5	20 mL	500	[202]
Multiple-column chromatography	80	0.7	200 µL		[201]
Solvent extraction	89	0.5	10 mL	1000	[202]
Precipitation of bulk target as $SrSO_4$	88	0.9	500 µL	15000	[197]

coprecipitation followed by ion-exchange chromatography appears to lead to the product of the highest chemical purity. So far the maximum batch yield of about 3.5 GBq was also reported using that method [139]. The two-step electrolytic process is also very useful [141, 196].

The radionuclide ^{86}Y has become the most important imaging nuclide for quantification of radiation dosimetry of ^{90}Y-labelled therapeutics [67], although many spurious coincidence corrections are needed [204]. Due to the ever increasing demand for this radionuclide, its large-scale production via the ^{86}Sr(p,n)^{86}Sr reaction is either already established or is being planned at several centres. On the other hand, its production at a few hospital-based cyclotrons has also been achieved using a solution target [199]. The yield is low but it may be enough for local use.

^{89}Zr ($T_{½}$ = 3.27 d)

This radionuclide is one of the most promising metallic radionuclides for developing new agents for immuno-PET. The positron emission intensity of only 22.3% is rather low, but due to the relatively low positron endpoint energy, the resolution of PET scans is high and comparable to that of ^{64}Cu.

For production of this radionuclide, several nuclear reactions have been investigated. However, the method of choice is the ^{89}Y(p,n)^{89}Zr reaction. The target element is monoisotopic, the reaction cross section is high [cf. 69] and production can be carried out at a small-sized medical cyclotron. The standardised method of its production [205, 206] consists of irradiation of a Y-metal foil with about 15 MeV protons for several hours at beam currents of about 15 μA. The chemical processing starts with dissolution of the target in HCl and separation of radiozirconium by use of a hydroxamate resin, followed by further purification steps. In fact, the most difficult part of the production process is the purification step. The product is obtained as [^{89}Zr]Zr-oxalate. Finally it is converted to chloride form and reconstituted in water or saline. In a typical production run the batch yield of ^{89}Zr amounted to 2 GBq. This amount is sufficient for most applications. However, for potential use in labelling of monoclonal antibodies (mAbs), the radionuclide should be of high specific activity. Despite the established production procedure, there are often difficulties in achieving the desired purity and specific activity. A recent publication [207] presents a simple scheme of separation of radiozirconium by ion-exchange chromatography using Dowex 1×8 resin and elution with 2 M HCl, whereby the product is obtained as $ZrCl_4$. The batch yield achieved was about 1 GBq. The radionuclidic purity was high but tests on its suitability for labelling work need to be demonstrated. In view of increasing significance of this radionuclide, several laboratories have developed solution targets. In order to avoid in-target salt precipitation, the use of Y$(NO_3)_3$ in dilute nitric acid solution has been recommended [118], and ^{89}Zr yields of up to 350 MBq have been reported.

^{94m}Tc ($T_{½}$ = 52.5 min)

This radionuclide is rather short-lived and the accompanying γ-ray at 871 keV creates some difficulty in PET measurement. Nevertheless, because of its high β^+ emission intensity and medium positron endpoint energy, it is used for quantifying ^{99m}Tc-SPECT scans. In fact this is the most suitable positron-emitting radionuclide of technetium. For its production, several routes have been investigated (for a review cf. [101]), but the ^{94}Mo(p,n)^{94m}Tc reaction over the energy range of E_p = 13 → 7 MeV was found to be the best. It is a high-yield process and the level of the ground state impurity (^{94g}Tc) is low. In general, a 94% enriched $^{94}MoO_3$ pellet was irradiated with protons at beam currents of about 5 μA. The chemical separation of radiotechnetium was done by extraction from alkaline solution with methylethylketone and a radiochemical yield of about 60% was achieved [208]. However, the thermochromatographic method using a vertical quartz apparatus (cf. Fig. 4.2) was found to be more suitable [135]. While using moist air as carrier gas, ^{94m}Tc was removed and deposited on the upper part of the quartz tube, from where it was collected in 5 mL of hot 10^{-4} M NaOH and quickly purified using a minimised alumina column (see Appendix V). The solution contained >99% $^{94m}TcO_4^-$ and the batch yield amounted to about 10 GBq. This thermochromatographic method of separation is now so established that it is often used in the separation of ^{99m}Tc produced via the ^{100}Mo(p,2n)^{99m}Tc reaction at a cyclotron.

^{124}I ($T_{½}$ = 4.18 d)

This radionuclide is somewhat longer lived and it has also a relatively low positron branching of 22.0% [37]. The β^+ endpoint energy amounts to 2137 keV and several γ-rays are associated with its decay. The radionuclide is thus not ideal for PET studies. Nonetheless, after applying certain γ-ray scattering corrections, it is possible to use it even in animal PET. For the production of ^{124}I, a large number of nuclear reactions have been investigated (for review cf. [72] and references to nuclear data cited therein). A summary is presented in Table 6.4. It was concluded that the ^{124}Te(p,n)^{124}I reaction over the energy range of E_p = 12 → 8 MeV is most suitable for the production of ^{124}I. The yield of ^{124}I is not very high but the product obtained is of the highest radionuclidic purity, the level of the associated long-lived ^{125}I ($T_{½}$ = 59.4 d) impurity being < 0.1%. Today, for clinical-scale production of ^{124}I this reaction is almost universally applied, and batch yields of a few GBq are obtained. The procedure commonly involves irradiation of a 99.8% enriched $^{124}TeO_2$ target and removal of radioiodine by a distillation process [112, 209–213] at 755 °C (cf. Fig. 4.1). Radioiodine is collected almost quantitatively in 0.3 mL of 0.02 M NaOH solution. Its radiochemical form is checked by high-performance liquid chromatography; it is generally > 98% iodide, which is very suitable for

Table 6.4: Routes for production of $^{124}I^{*}$.

Nuclear reaction	Energy range (MeV)	Thick target yield of ^{124}I[a] (MBq μAh^{-1})	Impurity (%)		
			^{123}I	^{125}I	^{126}I
^{124}Te(d,2n)	14 → 10	17.5	–	1.7[c]	–
^{124}Te(p,n)[b]	12 → 8	16	1.0	< 0.1[c]	–
^{125}Te(p,2n)	21 → 15	81	7.4	0.9	–
^{126}Te(p,3n)	36 → 26	190	148	1.3	1.0
^{121}Sb(α,n)	22 → 13	2.1	895	< 0.05[c]	< 0.16
^{nat}Sb(α,xn)	45 → 32	6.7	537	1.8[c]	0.6
^{123}Sb(α,3n)	45 → 32	15.5	236	1.8	0.6
^{123}Sb(^{3}He,2n)	19 → 13	0.73	11	0.6	0.6

[*] Information deduced from measurements and evaluations of cross-section data done at FZ (Jülich) in cooperation with ATOMKI (Debrecen), iThemba LABS (Cape Town), EAEA (Cairo) and GCU (Lahore).

[a] Calculated from the excitation function, assuming 100 % enrichment of the target isotope (unless mentioned otherwise) for an irradiation time of 1 h.

[b] This route gives the purest form of ^{124}I.

[c] Also validated by experimental measurement [112, 136, 137].

subsequent synthesis steps. The enriched target material is regenerated (without any substantial loss) for reuse. The radionuclide ^{124}I is widely used in tumour targeting as well as in thyroid dosimetry.

6.1.3 Emerging Non-standard Positron Emitters

Many of the non-standard positron emitters listed in Table 6.1 are interesting, but their use is as yet not so pronounced as of the established positron emitters described above. Some of them have been gaining more importance in recent years. They include ^{44g}Sc, ^{45}Ti, ^{61}Cu, ^{73}Se, ^{76}Br and ^{152}Tb. Their production methods are described below.

^{44g}Sc ($T_{½}$ = 3.9 h)

This radionuclide has a suitable half-life, a high positron emission intensity and not a too high positron endpoint energy. It is thus very useful for preparing metal complexes for functional studies using PET. Furthermore, it forms an excellent theranostic pair with the therapeutic radionuclide ^{47}Sc ($T_{½}$ = 3.35 d).

The production methods of ^{44g}Sc have been very recently reviewed [214]. Two routes are of interest:

a) $^{45}\mathrm{Sc(p,2n)}^{44}\mathrm{Ti}\,(60.4\,\mathrm{a}) \xrightarrow{EC} {}^{44g}\mathrm{Sc}$ generator system,
b) direct production via ^{44}Ca(p,n)^{44g}Sc or ^{44}Ca(d,2n)^{44g}Sc reaction.

The first route involves the production of the parent ^{44}Ti via the nuclear reaction ^{45}Sc(p,2n)^{44}Ti at an intermediate energy accelerator. However, due to its very long half-life, the production is a rather difficult proposition. Over the energy range of E_p = 35 → 15 MeV the calculated yield of ^{44}Ti amounts to ~4 kBq μAh^{-1}, calling upon a long irradiation of the target. To date only a 185 MBq generator has been reported [215, 216] (for more details see Appendix V), but extensive radiochemical work is underway [217, 218]. The separated ^{44g}Sc is free of ^{44m}Sc ($T_{½}$ = 2.44 d).

The second route makes use of highly enriched ^{44}CaO or $^{44}CaCO_3$ as target material [219, 220]. The product ^{44g}Sc is then separated by ion-chromatography and batch yields of up to 2 GBq have been reported [220]. Smaller amounts of ^{44g}Sc have been produced using the ^{44}Ca(d,2n)^{44g}Sc reaction [221, 222]. A drawback of the direct method is the formation of the longer lived isomeric state ^{44m}Sc in amounts of up to 2.5% of the ground state. On the other hand, this drawback is positively used in some laboratories to prepare a so-called in-vivo generator [223]. The longer lived ^{44m}Sc decays 100% by isomeric transition to ^{44g}Sc, which can be measured via PET. Further work on clinical-scale production of ^{44g}Sc is continuing. A new aspect of direct production of ^{44g}Sc is the use of a solution target [117], as described above for a few other non-standard positron emitters.

^{45}Ti ($T_{½}$ = 3.1 h)

This radionuclide has somewhat similar decay properties as ^{44}Sc and so it is very suitable for PET studies. However, due to its tetravalent character, its chemistry is different from that of scandium. Titanium(IV) complexes, particularly titanocene complexes, exhibit high antitumour activity. This radionuclide is thus of potential interest in tumour research.

The radionuclide ^{45}Ti is generally produced via the ^{45}Sc(p,n)^{45}Ti reaction [169, 224–226]. In a typical production experiment, natural Sc foil was irradiated with 14.5 MeV protons at about 10 μA beam current. Thereafter the foil was dissolved in 6 M HCl and transferred to a cation-exchange column filled with the resin AG 50W×8. On further treatment of the column with 6 M HCl, titanium was eluted as [-^{45}Ti]/HCl solution. It was evaporated to dryness and the ^{45}Ti residue was taken up in a desired solvent for further studies. Typically the batch yield of ^{45}Ti amounted to about 2 GBq and its radionuclidic purity to 99.8% A new approach under development is to separate this radionuclide as $^{45}TiCl_4$.

^{61}Cu ($T_{½}$ = 3.3 h)

This short-lived positron-emitting copper radionuclide is occasionally considered as an alternative to ^{64}Cu because it can be applied in smaller doses. However, the resolution of PET scans with ^{61}Cu is not as high as with ^{64}Cu due to the additional γ-rays and the higher positron endpoint energy of ^{61}Cu. Nevertheless, it has recently attracted some interest in a few laboratories.

A large number of nuclear reactions have been investigated to produce ^{61}Cu and the relevant data have been evaluated [227]. Three routes, namely, ^{61}Ni(p,n)^{61}Cu, ^{64}Zn(p,α)^{61}Cu and ^{59}Co(α,2n)^{61}Cu have been developed to achieve batch yields enough for clinical studies. The ^{61}Ni(p,n)^{61}Cu route is well established [65, 182] because the production methodology is the same as for ^{64}Cu, except that the target used is highly enriched ^{61}Ni instead of ^{64}Ni.

The production of ^{61}Cu via the ^{64}Zn(p,α)^{61}Cu reaction demands the use of highly enriched ^{64}Zn as target material to be able to achieve both the desired quality and quantity of the product. The electrolytic preparation of the target is similar to that for the production of radiogallium from zinc targets. The radiochemical separation of ^{61}Cu is achieved through ion-exchange chromatography. In a typical production run, the batch yield of ^{61}Cu amounted to about 1 GBq [228], with good radionuclidic purity and high specific activity.

The ^{59}Co(α,2n)^{61}Cu reaction for the production of ^{61}Cu is used if the α-particle beam of about 40 MeV is available. The target material is a monoisotopic metal that can withstand high beam currents. The irradiated target is dissolved in HNO_3 and separation of ^{61}Cu is effected either by a combination of cation- and anion-exchange chromatography or by using a chelating resin [229, 230]. In a typical production experiment, the batch yield of ^{61}Cu amounted to about 1.5 GBq [229] with 99.3% radionuclidic purity and good specific activity.

^{73}Se ($T_{½}$ = 7.1 h)

This radionuclide has a relatively high positron branching, the positron endpoint energy is not too high and only a few γ-rays are emitted. It is therefore suitable for a study of selenium metabolism in living systems via PET. Selenium is also an analogue of sulfur, which itself has no suitable positron emitting radionuclide. The radionuclide ^{73}Se could thus be utilized in the study of sulfur metabolism as well. However, due to the difficulty in production and chemical separation of ^{73}Se, its medical application has so far been very limited. For its production several nuclear processes were investigated (see Section 2.5.3). Recently a critical analysis of the cross-section data of all reactions was performed. The thick target yields were calculated [32] and the results are reproduced in Fig. 6.1. From those yields and also considering the levels of the associated longer lived impurities ^{75}Se ($T_{½}$ = 120.0 d) and ^{72}Se ($T_{½}$ = 8.5 d), it was concluded that the ^{75}As(p,3n)^{73}Se reaction over the energy

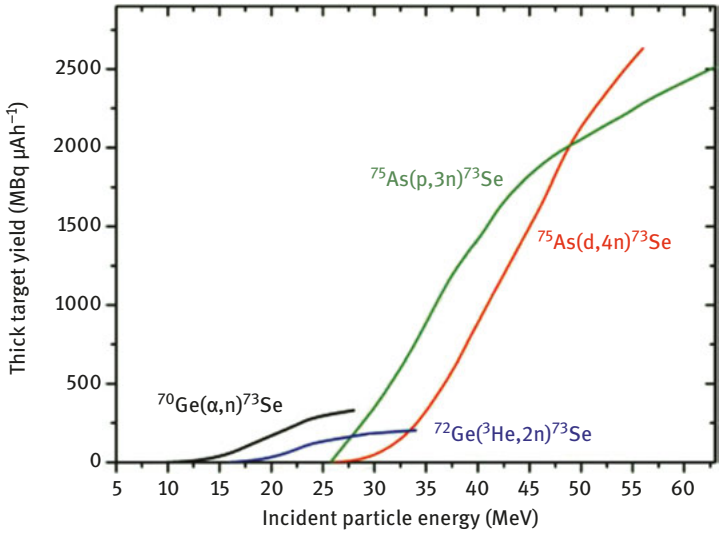

Fig. 6.1: Thick target yields of ^{73}Se calculated from the excitation functions of several reactions in the intermediate energy range given in Fig. 2.12. Taken from Qaim et al. [32], with courtesy of De Gruyter.

range of E_p = 40 → 30 MeV is most suited. The target used for production was either As_2O_3 or Cu_3As alloy. The separation of radioselenium from the As_2O_3 target was performed via ion-exchange chromatography [71]. A recently improved method makes use of solid phase extraction after selective complex formation with aminophthaline [231]. In contrast, the separation of radioselenium from the Cu_3As target was based on a two-step thermochromatographic process (see Fig. 4 in Appendix V and [133]), followed by extraction with benzene. Batch yields of about 6 GBq were achieved.

In case of nonavailability of a cyclotron with 40 MeV protons, the ^{70}Ge(α,n)^{73}Se reaction could be used as an alternative on a limited scale [134]. A high current $Cu_3{}^{70}$Ge target (using 99% enriched ^{70}Ge) was developed and irradiated at 80 μA beam of 28 MeV α-particles. The separation of radioactivity was performed via thermochromatography, followed by a further purification step. The batch yield amounted to 2 GBq. It should be mentioned that small amounts of ^{73}Se have also been produced using the intermediate energy reaction ^{nat}Br(p,x)^{73,75}Se [232].

^{76}Br ($T_{½}$ = 16.2 h)

This radionuclide has been under consideration for a long time. However, due to its high positron endpoint energy and due to the difficulty in its production, its use has been limited. In recent years, some new interest has developed.

For the production of ^{76}Br a large number of nuclear processes were investigated (see Appendices I, II and VII) and partly evaluated [233]. Out of those reactions ^{75}As(^{3}He,2n)^{76}Br and ^{76}Se(p,n)^{76}Br have been more often utilized. Regarding the first reaction, the high-current irradiation technology using a Cu_3As alloy target and the thermochromatographic separation of ^{76}Br are very well established [108, 234] and batch yields of about 600 MBq were obtained. However, due to the rare availability of the ^{3}He-particle beam, this method cannot be generally used. The emphasis is, therefore, on the ^{76}Se(p,n)^{76}Br reaction, which can be employed even at a small-sized cyclotron. The procedure, though very promising, is afflicted with great problems of targetry. The compound $Cu_2{}^{76}Se$ has proved to be the best and a thermochromatographic method of radiobromine separation has been developed [235], which is presently the method of choice. The ^{76}Br batch yield is limited to about 300 MBq. In a few recent studies, other target materials have also been critically evaluated [cf. [107, 236]. In particular, the newly proposed NiSe compound as target material is advantageous in that the radiobromine is completely removed from the distillation apparatus and collected in a water trap [236]. However, the utility of this procedure in a full production run using a highly enriched target has as yet not been demonstrated. Thus, constant development work is presently being pursued with respect to the production of this radionuclide in sufficient quantity and good quality.

^{152}Tb ($T_{½}$ = 17.5 h)

The radionuclide ^{152}Tb is the only suitable β^+ emitter in the region of lanthanides, which has been successfully developed for PET measurements. It can thus serve as an exact diagnostic match to the β^- emitting therapeutic radionuclide ^{161}Tb ($T_{½}$ = 6.9 d) as well as to the α-particle emitting ^{149}Tb ($T_{½}$ = 4.1 h). Its production methods have been very recently reviewed [214]. To date its production has been carried out via two very special methods:

(a) ^{12}C-induced reactions on ^{nat}Nd, producing ^{152}Dy that decays to ^{152}Tb. The final product was chemically separated using cation-exchange chromatography [98]. The batch yield amounted to a few MBq and was not sufficient for a PET phantom measurement.
(b) Spallation of ^{nat}Ta with 1000 MeV protons whereby the ^{152}Tb produced was first separated by an on-line mass separator and thereafter purified chemically [99]. Batch yields of about 150 MBq were achieved and its utility in human PET studies has been recently demonstrated [245].

The production of ^{152}Tb could also be done using the ^{155}Gd(p,4n)^{152}Tb reaction, but so far only reaction cross sections have been measured [254]. Further development work is continuing.

6.1.4 Other Potentially Useful Positron Emitters

In addition to the six established and six emerging non-standard positron emitters discussed above, several others listed in Table 6.1. have also been produced on a clinical scale. The respective nuclear reactions and the batch yields achieved are given in Table 6.1. Many of the radionuclides were produced only for local use, and the general interest has been shifting. Thus, the short-lived radionuclides ^{30}P, ^{34m}Cl and ^{38}K were produced almost exclusively using the α-particle beam [170, 173–175], the radionuclides ^{75}Br and ^{77}Kr using the ^{3}He-particle beam [108, 110] and the radionuclides ^{51}Mn and ^{55}Co using the deuteron beam [176, 181]. Small amounts of ^{52}Fe were also produced using the ^{3}He- and α-particle beams [240, 241]. Most of the other radionuclides could be produced using the proton beam of varying energy. Over the energy range below 20 MeV, for example, the (p,n) reaction was used to produce ^{38}K [172], ^{66}Ga [237], ^{82m}Rb [120], ^{90}Nb [239] and ^{120}I [54, 112], and the (p,α) reaction to produce ^{55}Co [109] and ^{75}Br [238, 246]. Over the energy range above 25 MeV, the (p,xn) reactions were utilized to produce ^{38}K, ^{52}Fe, ^{44}Ti (parent of ^{44}Sc), ^{62}Zn (parent of ^{62}Cu), ^{72}Se (parent of ^{72}As), ^{81}Rb, ^{83}Sr, and ^{140}Nd (parent of ^{140}Pr) (for references see Table 6 1.).

In conclusion, it may be added that the production technology of non-standard positron emitters is developing very fast. Hitherto the batch yields are limited for the established non-standard radionuclides to about 40 GBq, and for the others to about 1 GBq. With emerging novel applications, continuous research and development work is underway to improve the known methods or to investigate newer methods of production, the main criteria being the yield, the purity and the specific activity of the desired radionuclide.

6.2 Novel Radionuclides for Internal Radiotherapy

The number of potentially useful therapeutic radionuclides is very large. However, as mentioned above, the present emphasis is on radionuclides emitting highly ionizing low-range radiation. In this connection, a particular demand is on the chemical purity and specific activity of the radionuclide under investigation, especially if it is of metallic nature. Many of the novel therapeutic radionuclides have been occasionally discussed (see Appendices IV and VI). The scope of this section is limited to a few typical novel radionuclides, emitting low-energy β^- particles, α-particles, conversion electrons or Auger electrons. A summary is given in Table 6.5. The references given therein deal specifically with the production aspects [256–290]. Some of those radionuclides were previously produced in a nuclear reactor. The trend is now shifting over to the use of accelerators. However, in contrast to novel β^+ emitters, the production of many of the novel therapeutic radionuclides demands an accelerator/cyclotron delivering intermediate energy protons/deuterons and/or

Table 6.5: Production methods of some novel therapeutic radionuclides.*

Radionuclide	Decay data				Major production routes and relevant data					
	$T_{1/2}$	Radiation of interest (%)	Energy[a] (keV)	Major γ-ray energy in keV (%)	Nuclear reaction	Energy range (MeV)	Thick target yield[b] (MBq μAh^{-1})	Target material, enrichment (%)	Typical batch yield (MBq)	References to production work
^{47}Sc	3.35 d	β^- (100)	610	159 (68)	^{47}Ti(n,p)[g]	Reactor neutrons	4.8 × 10^3/(g h)[c]	$^{47}TiO_2$ (96.4)	1.6 × 10^3	[256]
					$^{46}Ca(n,\gamma)^{47}Ca \xrightarrow{\beta^-} {}^{47}Sc$	Reactor neutrons		$^{46}Ca(NO_3)_2$ (31.7)	600	[257]
					^{48}Ti(γ,p)	Photons: 40		$^{nat}TiO_2$	186	[260]
^{67}Cu	2.58 d	β^- (100)	577	185 (48.6)	^{67}Zn(n,p)	Reactor neutrons	0.44/(g h)[d]	^{67}ZnO (93.0)	1.1 × 10^3	[cf. [79]
					^{68}Zn(γ,p)	Photons, 40	1.0/(g kW h)[e]	ZnO	185	cf. [79, 258, 259]
					^{70}Zn(p,α)[g]	18 → 12	2.2	^{70}Zn electroplated (70)	14	[263]
					^{68}Zn(p,2p)[g]	80 → 30	42	^{68}ZnO (99.7)	1.6 × 10^3	[268]
^{186}Re	3.78 d	β^- (92.5) EC (7.5)	1070	137 (9.5)	^{186}W(p,n)[g]	18 → 5	4	$^{186}WO_3$ (99.9)	<200	[276]
								WS_2		[278]
					^{186}W(d,2n)[g]	18 → 9	16	W, WO_3	<100	[274]
^{149}Tb	4.1 h	α (16.7) β^+ (4.3) EC (79)	3970	165 (27.8) 352 (33.0)	^{165}Ho(p,spall)	~1000	5.8[f]	Ta, Ho	<200	[99, 282]
					Nd(^{12}C,xn)	100 → 80	2.5[f]	Nd	~10	[98]
^{225}Ac	10.0 d	α (100)	5830	100 (1.7)	^{226}Ra(p,2n)	22 → 10	7	^{226}RaCl	500	[81]
					^{232}Th(p,x)	140 → 60	4	in development		[82-86]

(continued)

Table 6.5 (continued)

^{117m}Sn	13.6 d	IT (100) Conversion electrons	156	159 (86.4)	^{nat}In(α,pxn) ^{116}Cd(α,3n)^{g}	45 → 20 60 → 30	0.3 x10^{-3} 8.4	In metal ^{116}Cd metal (98.8)	~10 2 × 10^{3}	[286] [285]
^{193m}Pt	4.33 d	IT (100) Auger electrons	10 - 130	136 (0.11)	^{192}Pt(n,γ)^{g} ^{192}Os(α,3n)^{g}	Fission spectrum 40 → 30	 10	 ^{192}Os electroplated (99.6)	i, h 10	 [288]
^{195m}Pt	4.02 d	IT (100) Auger electrons	10 - 130	99 (11.4)	^{194}Pt(n,γ) ^{195}Pt(n,n´γ)^{195m}Pt ^{193}Ir(n,γ)^{194}Ir ^{194}Ir(n,γ)^{195m,g}Ir $\rightarrow_{\beta^-}$ ^{195m}Pt ^{192}Os(α,n)^{g}	Fission spectrum Fission spectrum Fission spectrum 28 → 15	 0.1	 ^{192}Os electroplated (99.6)	i, h i, h j < 5	 [289]

* Adapted partly from Qaim [36], with permission from Elsevier, and extended for production data.
[a] For β^-, the values are maximum energies.
[b] Calculated from the excitation function, unless otherwise stated, for an irradiation time of 1h.
[c] Experimental yield in a high flux reactor using an enriched target.
[d] Experimental yield in a medium flux reactor, using a ^{nat}Zn target.
[e] Experimental yield using a ^{nat}Zn target
[f] Experimental yield (MBq) of product.
[g] Using highly enriched isotope as target material.
[h] Low specific activity.
[i] sufficient batch yield for application.
[j] Production not yet explored (see text).

α-particles. Efforts are also underway in some laboratories to produce a few of those radionuclides using fast neutrons and intense photon sources.

6.2.1 Novel Low-Energy β^- Emitters

^{47}Sc ($T_{1/2}$ = 3.35 d)

This radionuclide decays 100% by β^- emission with the endpoint energy of 610 keV. It is gaining importance as a β^- theranostic pair of the β^+ emitter ^{44g}Sc (or also ^{43}Sc). Being a trivalent metal, scandium forms good chemical complexes with many oxygen-containing bifunctional chelators which are potentially useful for internal radiotherapy. The methods for its production in no-carrier-added form have been recently reviewed [214]. The main production route so far has been the ^{47}Ti(n,p)^{47}Sc process in a nuclear reactor. Several groups attempted to produce this radionuclide using a ^{nat}Ti target. Although the chemical procedures developed to separate radioscandium were fairly successful, the radionuclidic purity achieved was not acceptable. By irradiating a highly enriched $^{47}TiO_2$ target in a high neutron flux reactor at the Brookhaven National Laboratory, the method could be successfully used. The separation of radioscandium was done by ion-exchange techniques and high-purity ^{47}Sc was achieved in batch yields of about 1.5 GBq [256].

Some efforts have also been devoted to the possible production route $^{46}\mathrm{Ca}(\mathrm{n},\gamma)^{47}\mathrm{Ca}\xrightarrow{\beta^-}{}^{47}\mathrm{Sc}$. Due to very low abundance of ^{46}Ca (0.004%) in ^{nat}Ca and due to the relatively low (n,γ) cross section, the yield of ^{47}Sc achieved was very low. However, by irradiating a 31.7% enriched $^{46}Ca(NO_3)_2$ target in the high neutron flux reactor at Grenoble, combined with a clean chemical separation of radioscandium from calcium, a batch yield of 0.6 GBq of ^{47}Sc was obtained [257].

In recent years, there has been an increasing interest in the utilization of electron linear accelerators for medical radionuclide production (see Section 3.4). Some studies on the possibility of production of ^{47}Sc via the ^{48}Ti(γ,p)^{47}Sc reaction have been going on for some time [103, 258–260] and very recently ^{47}Sc has been produced via this route at the Argonne National Laboratory in batch yields of about 185 MBq [260].

The production of ^{47}Sc via charged-particle induced reactions has also been under investigation. For example, the reaction ^{48}Ti(p,2p)^{47}Sc was studied, but the yield was very low. Another possible production route is the ^{44}Ca(α,p)^{47}Sc reaction. In a feasibility study using a 97% enriched ^{44}CaO target and a 28 MeV α-particle beam at the NIRS Chiba, highly pure ^{47}Sc in a batch yield of 11 MBq was achieved [261]. This production method should be interesting for obtaining ^{47}Sc for local use. For increasing the yield, high-current targetry needs to be developed.

In summary, considerable further research and development work is essential to obtain ^{47}Sc in sufficiently high yield and medically acceptable purity.

^{67}Cu ($T_{½}$ = 2.58 d)

This radionuclide also decays 100% by β^- emission with the endpoint energy of 577 keV. It is gaining enhanced attention for use as a theranostic pair of the β^+ emitter ^{64}Cu (see above). The radionuclide has been under consideration for more than 40 years and the knowledge available till 2011 was critically reviewed [79], supplemented later by some other reviews [36, 72, see also Appendix VI]. Similar to ^{64}Cu, the reactor production of ^{67}Cu is not very fruitful. As mentioned in Section 2.5.5, four routes using charged particles appear to be promising for the production of ^{67}Cu. They are ^{70}Zn(p,α)^{67}Cu, ^{70}Zn(d,αn)^{67}Cu, ^{64}Ni(α,p)^{67}Cu and ^{68}Zn(p,2p)^{67}Cu. A detailed review of the production possibilities using those reactions has been recently published [214]. The first two reactions can be used at a low-energy cyclotron, the third one at a medium-sized cyclotron with an α-particle beam and the last one at an intermediate-energy cyclotron or accelerator. The thick target yields calculated from their cross-section data are given in Fig. 6.2., which is an updated version of Ref. [167]. Evidently the ^{68}Zn(p,2p)^{67}Cu reaction is more suitable. The low-energy reactions ^{70}Zn(p,α)^{67}Cu and ^{70}Zn(d,αn)^{67}Cu were investigated for practical production [262–264], but the batch yield was small. The interaction of protons with ^{70}Zn at about 60 MeV may lead to higher yield of ^{67}Cu due to the expected high cross section of the ^{70}Zn(p,2p2n)^{67}Zn process. Very recently the ^{64}Ni(α,p)^{67}Cu reaction [265, 266] was used to produce small amounts of ^{67}Cu for preclinical studies [267]. Presently work is underway in a few laboratories to develop the ^{68}Zn(p,2p)^{67}Cu

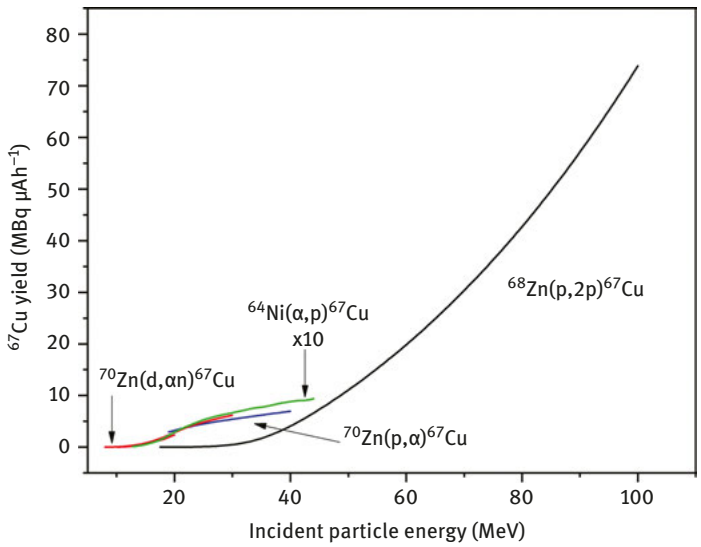

Fig. 6.2: Integral yields of ^{67}Cu from several charged-particle induced reactions, calculated from the excitation functions given in Refs. [41, 264–266].

production route using about 80 MeV protons [268] on an enriched ^{68}Zn target. A ^{nat}Zn target and also proton energies beyond 80 MeV, even on an enriched ^{68}Zn target, lead to considerable formation of stable ^{65}Cu, which decreases the specific activity of ^{67}Cu. The chemical separation of ^{67}Cu is generally done by ion-exchange chromatography, and batch yields of a few GBq have been achieved [268]. More efforts are needed to increase the yield.

In recent years, similar to ^{47}Sc (see above), attempts have been made to utilize high-energy photon sources to produce ^{67}Cu via the reaction ^{68}Zn(γ,p)^{67}Cu [cf. [258, 259]. The yield is rather low and the present-day photon sources are not capable of delivering the radionuclide in the required quantity. Nevertheless, with intensified technological efforts, the feasibility of production of appreciable quantities of ^{67}Cu via this route has been demonstrated at the Idaho Accelerator Centre and the Argonne National Laboratory. In parallel, the use of intense fast neutron sources to produce this radionuclide is being extensively pursued at the Japan Atomic Energy Research Institute. Using a 50 MeV deuteron breakup neutron source (see Chapter 3), the reaction ^{68}Zn(n,np)^{67}Cu has been investigated and ^{67}Cu of high purity has been obtained in quantities sufficient for preclinical studies [129]. Development of more powerful fast neutron sources should lead to higher yields of ^{67}Cu. A further newer approach is to harvest ^{67}Cu from the cooling loop of the Facility for Rare Isotopes under construction in the United States [cf. [269]. The question whether the photon and neutron induced reactions or parasitic production sources would lead to ^{67}Cu in yields and purity comparable to that via the (p,2p) reaction is presently open. Further extensive efforts are needed to improve the availability of this very important radionuclide.

^{186}Re ($T_{½}$ = 3.78 d)

Because of similarity in Tc and Re chemistry, the radionuclide ^{186}Re is attractive for internal radiotherapy. A real theranostic application of this radionuclide, however, cannot be achieved because of lack of availability of a positron emitting isotope of Re. Nevertheless, there is optimism that the therapeutic uptake of this radionuclide could be determined through SPECT imaging.

Due to the low specific activity of ^{186}Re achieved via the ^{185}Re(n,γ)^{186}Re reaction, and due to the short half-life and rather high β^- endpoint energy of 2110 keV of the generator-produced ^{188}Re (see Chapter 5), the emphasis got-shifted over the last 20 years towards the development of ^{186}Re of high specific activity using a cyclotron. So far two nuclear routes have been successfully applied for its production. They are ^{186}W(p,n)^{186}Re and ^{186}W(d,2n)^{186}Re. Most of the studies have dealt with nuclear reaction cross-section measurements (for references to original literature see [41, 80] and Appendix VII). A critical analysis of data showed [80] that, for obtaining a high-purity product, an enriched ^{186}W target is absolutely necessary. The theoretical yields of ^{186}Re calculated

from the evaluated excitation functions of the two reactions were reported (see Fig. 4 in Appendix IV and further updates [41, 80]). The yield via the (d,2n) reaction is higher. Experimentally, yields of the two reactions have been accurately measured [270]. The (d,2n) reaction thus appears to be more suitable if deuterons of the required energy and intensity are available. The yields from both the reactions are, however, much lower than those normally expected from the (p,n) and (d,2n) reactions in this mass region. This is due to the existence of the long-lived high-spin isomer ^{186m}Re ($T_{½}$ = 2×10^5 a, I = 8$^+$), which is more favourably populated than the low-spin isomer ^{186}Re (I = 1$^-$). Thus, high-current beams are needed to compensate for the low yield of the reaction product.

In recent years, strong efforts are being devoted to develop suitable target materials for the production of ^{186}Re. Studies have been reported on the use of W metal [271–274], WO_3 [274–276], WC [277] and WS_2 or OsS_2 [278]. For separation of radiorhenium, dry distillation, liquid–liquid extraction and ion-exchange chromatography have been successfully applied. Further detailed chemical separations are being devised.

Based on nuclear model calculations, the expected specific activity of ^{186}Re was predicted [80]. In more recent experiments, attempts were made to achieve high specific activity of ^{186}Re [270, 276, 280, 281]. High-current targetry and efficient separation methods are in development to produce this radionuclide in quantities sufficient for medical applications. A clinical-scale production has hitherto not been reported.

6.2.2 Novel α-Particle Emitters

Several α-particle emitting radionuclides have been attracting attention for their possible use in α-targeted therapy. The radionuclides already in clinical use, namely, ^{211}At, ^{223}Ra and ^{225}Ac, have been discussed in Chapter 5. The radionuclide ^{230}U ($T_{½}$ = 20.8 d, 100% α-emission; $E_α$ = 5888 keV) is of some interest and its production has been studied (for original references, see Appendix VI). There are many other potentially useful α-emitters. More effort has been devoted in recent years to ^{149}Tb and ^{225}Ac and further work is continuing. A brief discussion of production routes of those novel radionuclides presently in development is given below.

^{149}Tb ($T_{½}$ = 4.1 h)

This is a rather exotic α-particle-emitting lanthanide and has so far found some limited application. The α-branching is only 16.7%. However, due to the relatively low energy of 3970 keV of the α-particle and the good complex chemistry of lanthanides, it is of great potential interest in α-targeted therapy. For its production two nuclear routes, namely, ^{142}Nd(^{12}C,5n)^{149}Dy → ^{149}Tb and ^{165}Ho(p,spall)^{149}Tb,

have been utilized. In the first, tracer quantities of radioterbium were chemically separated by ion-exchange chromatography. In the second, on-line mass separation was done at CERN and the applicability of this radionuclide in therapeutic studies was demonstrated [282, 283]. Further optimisation work assured its higher production yield [99]. A possible third route, namely, ^{152}Gd(p,4n)^{149}Tb reaction, has also been investigated up to proton energies of 66 MeV, but so far only reaction cross sections were measured [254]. Another potentially interesting reaction is ^{155}Gd(p,7n)^{149}Tb, which has hitherto not been investigated. It could be induced by about 120 MeV protons, and the cross section is expected to be high (cf. [36]). In summary, with the increasing significance of this radionuclide, intensified efforts would be needed to make it more generally available for preclinical work.

^{225}Ac ($T_{½}$ = 10.0 d)

Considerable interest has been aroused in recent years in this α-particle emitting radionuclide. Its characteristics and method of production via isolation from nuclear waste have already been described in Chapter 5 (Section 5.5.4). Presently two cyclotron production routes, namely, ^{226}Ra(p,2n)^{225}Ac and ^{232}Th(p,spall)^{225}Ac, are receiving considerable attention. The use of the ^{226}Ra(p,2n)^{225}Ac reaction [81] for the production of ^{225}Ac is extremely challenging because the target material is an α-particle-emitting radioactive isotope. Furthermore, the radionuclide ^{222}Rn ($T_{½}$ = 3.8 d) is formed in the decay of ^{226}Ra. Since it is an inert, diffusible gas under standard ambient conditions, there is a significant danger of contamination. The production technology for ^{225}Ac therefore demands specially conditioned irradiation and chemical processing laboratories. The optimum energy range for the production of ^{225}Ac via this route is E_p = 22 → 10 MeV and the calculated thick target yield amounts to 7 MBq μAh^{-1}. Based on their pioneering work at Karlsruhe, Apostolidis et al. [81] described the basic technology for its production in quantities of about 500 MBq. Further technological development is continuing to commercialize the production procedure.

A major thrust in relation to ^{225}Ac production today is being directed to the ^{232}Th(p,spall)^{225}Ac process [82–86]. The optimum energy range for this route is E_p = 140 → 60 MeV and the thick target yield of ^{225}Ac calculated from the excitation function amounts to about 4 MBq μAh^{-1}. Since worldwide only a few accelerators in this energy range are available, a concerted collaborative action in this direction would be very useful. The chemical processing of the target to isolate ^{225}Ac from the other spallation products is also challenging. The ^{227}Ac impurity ($T_{½}$ = 21.8 a) level in ^{225}Ac produced needs to be carefully controlled (see Appendix VII). Presently work on purification of radioactinium impurities is continuing [cf. [82, 84, 284].

Two other efforts to produce ^{225}Ac involve the study of formation of ^{225}Ra ($T_{½}$ = 14.8 d), which is the parent of ^{225}Ac. To this end, attempts are being made to

separate ^{225}Ra from the ^{232}Th(p,spall) products. On the other hand the photonuclear reaction $^{226}\mathrm{Ra}(\gamma,\mathrm{n})^{225}\mathrm{Ra}\xrightarrow{\beta^-}{}^{225}\mathrm{Ac}$ has also been suggested. Considering the presently on-going strong discussion on the development of powerful photon sources for medical radionuclide production, it may be worthwhile to pay attention to this route, though the problem of handling the radioactive target ^{226}Ra, as in the case of the ^{226}Ra(p,2n)^{225}Ac process, will remain. In any case, all suggested methods of production of ^{225}Ac demand extensive development work.

6.2.3 Novel Conversion and Auger Electron Emitters

The number of low-energy electron emitters is very large, but only a few have found medical application. In many cases, the intensity of Auger electrons is too weak to cause any noticeable therapeutic effect. Three radionuclides previously used in medical diagnostic studies via SPECT, namely, ^{67}Ga, ^{77}Br and ^{111}In, are now more of potential interest for Auger therapy. The production methods of ^{67}Ga and ^{111}In have been described in Chapter 5, and an early review on the methods for the production of ^{77}Br is given in Appendix II. Some more recent experimental and standardisation studies related to ^{77}Br are given in Refs. [78, 167]. The method of choice for its production remains the old reaction ^{75}As(α,2n)^{77}Br over the energy range of E_α = 30 → 20 MeV, and batch yields of about 2 GBq have been reported. In this section, only three radionuclides in development, namely, ^{117m}Sn, ^{193m}Pt and ^{195m}Pt, are briefly discussed and their production routes are described.

^{117m}Sn ($T_{½}$ = 13.6 d)

The decay and production data of the high-spin isomeric state (I = 11/2$^-$) of ^{117m}Sn have been partly discussed in Chapter 2 (Section 2.5.5). Due to the emission of low-energy conversion electrons, ^{117m}Sn is unique among all beta emitting radionuclides. Besides its production in a nuclear reactor, efforts are being devoted to obtain it with high specific activity via charged-particle induced reactions. The integral yields of ^{117m}Sn calculated from the excitation functions of those reactions are shown in Fig. 6.3. The ^{116}Cd(α,3n)^{117m}Sn reaction gives a high yield, amounting to about 8.4 MBq μAh^{-1} over the energy range E_α = 60 → 30 MeV. This reaction utilizing a highly enriched target is therefore very suitable for the production of no-carrier-added ^{117m}Sn. An ion-chromatographic method of separation of radiotin from a ^{116}Cd target has been developed for commercial production [285]. On the other hand, for production of small amounts of ^{117m}Sn for tracer studies, the reaction ^{115}In(α,d)^{117m}Sn at α-particle energies of about 30 MeV is also interesting. The yield is by a factor of about 15 lower than that from the (α,3n) reaction, but the advantage is that an enriched target is not needed. Furthermore, a simple dry

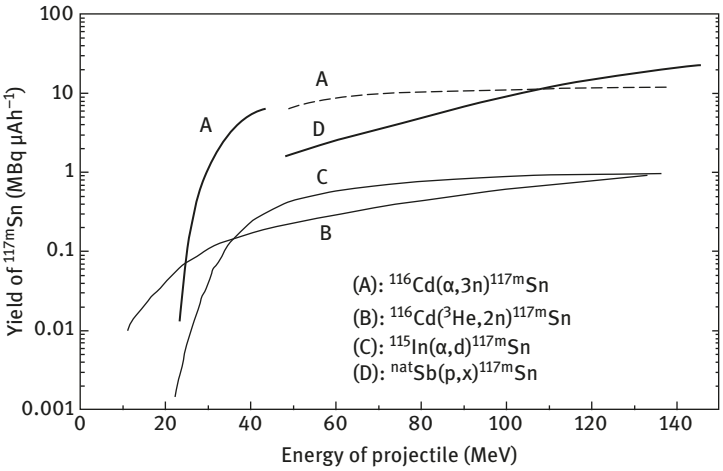

Fig. 6.3: Integral yields of ^{117m}Sn calculated from the excitation functions of several reactions in the intermediate energy range. The curve for the ^{nat}Sb(p,x)^{117m}Sn process describes experimental values. Taken from Qaim [36], with permission from Elsevier.

distillation method for the separation of ^{117m}Sn from an In target was developed [286]. The reaction ^{nat}Sb(p,x)^{117m}Sn is also useful if protons of energy above 80 MeV are available [287]. The chemical purity of the product achieved, however, has so far not been very satisfactory. The ^{116}Cd(α,3n)^{117m}Sn reaction is thus presently the method of choice. In view of the increasing demand for this radionuclide, an upscaling of the production procedure appears to be mandatory. It is being vigorously pursued at the Clear Vascular, Inc., USA.

^{193m}Pt ($T_{½}$ = 4.33 d) and ^{195m}Pt ($T_{½}$ = 4.02 d)

Since platinum complexes (like cis-di-chlorodiaminplatinum) have been in use in chemotherapy as potent antitumour agents for a long time, both ^{193m}Pt and ^{195m}Pt have great potential in Auger electron therapy. So far the major drawback in their wide-spread use was their non-availability with a high specific activity. The calculated yields of the two radionuclides via the ^{192}Os(α,3n)^{193m}Pt and ^{192}Os(α,n)^{195m}Pt reactions, respectively, are reproduced in Fig. 6.4. [32]. The yield of ^{193m}Pt via the ^{192}Os(α,3n)^{193m}Pt reaction over the energy range E_α = 40 → 30 MeV is fairly high. In small production runs, 99.65% enriched ^{192}Os was electroplated on a 10 μm thick Ni foil and irradiated with 38 MeV α-particles, followed by isolation of radioplatinum via distillation and solvent extraction techniques [288]. The batch yield of ^{193m}Pt was about 10 MBq [288]. The product was found to be of high radionuclidic purity and specific activity. An upscaling of this production process should lead to clinically interesting quantities.

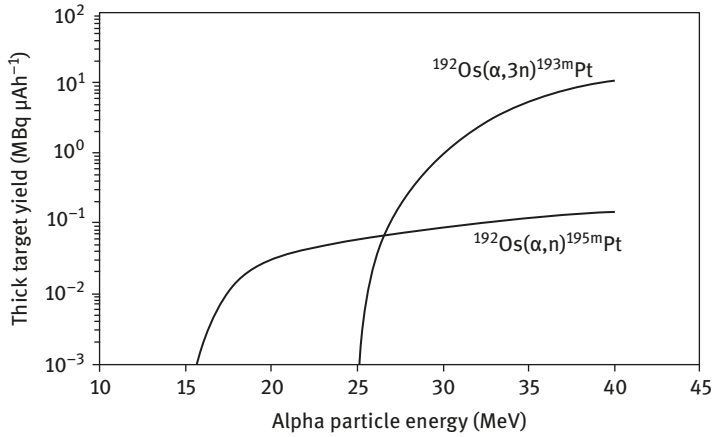

Fig. 6.4: Integral yields of ^{193m}Pt and ^{195m}Pt calculated from the excitation functions [58, 289]. Taken from Qaim et al. [32], with courtesy of De Gruyter.

With regard to ^{195m}Pt, in contrast to the ^{194}Pt(n,γ)^{195m}Pt and ^{195}Pt(n,n´γ)^{195m}Pt reactions (cf. [87]), the ^{192}Os(α,n)^{195m}Pt process gives higher specific activity, but the yield is low [289]. Thus, development of a high-current target is needed to compensate for the low yield. The idea to produce it via double neutron capture by ^{193}Ir and subsequent decay of the product to ^{195m}Pt (i.e., via the route $^{193}\mathrm{Ir}(\mathrm{n},\gamma)^{194}\mathrm{Ir}(\mathrm{n},\gamma)^{195\mathrm{m,g}}\mathrm{Ir}\xrightarrow{\beta^-}{}^{195\mathrm{m}}\mathrm{Pt}$) has not been investigated in detail. Nevertheless, the development of this route as well as the development of the (α,n) route (mentioned above) appear to be worthwhile for obtaining no-carrier-added ^{195m}Pt in sufficient yield.

6.3 Enhanced Use of SPECT in Imaging

As discussed above, PET imaging is preferred because of its quantitative nature. Due to this reason, a real theranostic application in medicine involves the use of two radionuclides of the same element, one emitting positrons and the other corpuscular radiation. In recent years, however, the tendency is increasing to use only the therapeutic radionuclide and to determine its organ uptake by registering an associated γ-ray via SPECT. This is not an ideal way because the radionuclide is only localised and not quantified (as in PET). Nevertheless, with the improving fastness and resolution in SPECT imaging combined with the much lower cost involved in it than that in PET, the newer approach appears reasonable for routine patient care studies, provided the therapeutic radionuclide emits a γ-ray of suitable energy and intensity for SPECT imaging. The application of SPECT could thus be in two directions:

a) Auger therapy: Auger and other low-energy electron emitters generally also emit a suitable γ-ray, for example, ^{67}Ga, ^{77}Br, ^{111}In and ^{117m}Sn, thereby allowing the use of SPECT. However, ^{125}I and ^{193m}Pt cannot be assayed by SPECT because no suitable γ-ray is emitted.
b) β^- therapy: Many of the conventional β^- emitting radionuclides emit a γ-ray, which allows SPECT imaging, for example, ^{177g}Lu. A few novel therapeutic radionuclides like ^{47}Sc and ^{186}Re also emit a suitable γ-ray whose compatibility with SPECT measurement has been demonstrated (cf. [276]). On the other hand, SPECT is not applicable to pure β^- emitters, for example, ^{32}P, ^{89}Sr and ^{90}Y.

In general, there is more reliance on SPECT while using a heavy mass metallic radionuclide, because very little work has been reported in that mass region with regard to production of positron emitters in tracer quantities. One radionuclide worth mentioning is ^{147}Gd ($T_{½}$ = 38.1 h), which was produced via the ^{147}Sm(^{3}He,3n)^{147}Gd reaction [290]. It is useful for a combination of MRI with SPECT, because Gd is an important contrast agent in MRI. Further development work will possibly lead to more extended use of SPECT imaging of heavy mass nuclei.

6.4 Concluding Remarks about Novel Medical Radionuclides

The above discussion shows that considerable efforts are being harnessed to develop novel radionuclides, with emphasis on non-standard positron emitters for special diagnostic studies and low-range β^- and α-particle emitters for targeted internal therapy. New facilities are being established, not only for irradiations with charged particles but also with fast neutrons and high-energy photons. Work is progressing in all directions, that is, nuclear data, high-current targetry, chemical processing and quality assurance methods. The demands on radionuclidic and chemical purity as well as on specific activity are increasing. In short, the field of production and medical application of novel radionuclides is fast expanding. It is thus a dynamic area of research. The related future perspectives are discussed in the next chapter.

7 Future Directions and Perspectives

Starting with the *tracer principle* formulated by Georg von Hevesy in the mid 1930s, the production of radionuclides for internal use in humans has made tremendous progress, and today a variety of products are available for patient care studies. In fact radioactivity has revolutionized medicine, both with regard to diagnosis and therapy. Through the advent of *tomographic techniques* (PET and SPECT) and use of suitable radionuclides it is now possible to study organ functions dynamically at a real molecular level. Similarly, great advances have been achieved in localisation and killing of tumour through *radionuclide targeted therapy*. Nevertheless, being a dynamic field, further research and development work is continuing. This entails commissioning of new irradiation facilities, development of newer technologies and continuous analysis of new directions in radionuclide applications. All those areas are briefly discussed below.

7.1 New Irradiation Facilities

The production of standard radionuclides will strongly depend also in the future on research reactors as well as on small- and medium-sized cyclotrons. In recent years, a few purely research-oriented nuclear reactors are being adapted partly to sample irradiations for radionuclide production. In addition, several new research reactors are being constructed with facilities for medical radionuclide production. Furthermore, big efforts are underway to establish PET centres for patient care studies in various parts of the world, and about 1000 level III medical cyclotrons are being installed. In addition, a network of medium-sized cyclotrons is being established, mainly in Canada, to promote accelerator production of ^{99m}Tc.

For development of novel research-oriented radionuclides, in addition to the established systems, newer irradiation facilities in the following three directions are expected to gain more significance (see also Section 2.5.7 and [36]):

- Intermediate energy accelerators with multiparticle beams
- High-energy and high-intensity photon sources
- Fast neutron sources based on deuteron breakup and spallation processes

With regard to *intermediate energy accelerators*, the demands for proton beams of energies up to about 150 MeV are increasing. Moreover, higher energy protons (1-2 GeV) in combination with on-line mass separation may find enhanced application in production of some special radionuclides. The α-particle beam is of great advantage in populating low-lying high-spin isomeric states of a few radionuclides that are of interest in Auger therapy. Furthermore, even heavy-ion-induced reactions could be utilized occasionally to produce some rare radionuclides in tracer quantities.

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Regarding *high-intensity photon sources*, the electron linear accelerator technology is well proven, and its further development to achieve high-power photon sources is being vigorously followed in a few laboratories. It is expected that photon sources will find more application in the production of a few selected radionuclides via (γ,n) and (γ,p) reactions.

As far as *fast neutron sources* are concerned, the breakup of 40 or 50 MeV deuterons on Be or C provides a hard neutron spectrum, which could be used for production of several special radionuclides via (n,p) and (n,n´p) processes. The same way it is expected that the spallation neutrons could also be advantageously used to induce the (n,p) reaction for radionuclide production purposes [36]. On a limited scale, the secondary neutrons produced in the interactions of intermediate energy protons with various target materials could be used to produce a few radionuclides via the (n,γ) reaction, especially if access to a reactor is not available.

Thus, presently strong efforts are being devoted to develop versatile newer irradiation facilities to meet the increasing challenges in medical radionuclide production. This enhanced interest is opening up new perspectives for related work.

7.2 Novel Technological Developments

The four basic pillars of radionuclide development technology, namely nuclear data, high-current targetry, efficient chemical processing and quality assurance of the radionuclide produced (see Chapters 2–4) have all been receiving enhanced attention in recent years, especially with respect to production of novel radionuclides using accelerators.

Regarding *nuclear data*, extensive reaction cross-section measurements as well as data evaluations have been done up to about 50 MeV. With increasing use of intermediate energy charged particles and high energy photons and neutrons, the available databases for medical radionuclide production will have to be strengthened. Also the decay data of several potentially useful therapeutic radionuclides, especially in the region of lanthanides, need to be improved. Even in reactor production of radionuclides, several (n,γ), (n,n´γ) and double neutron capture processes need to be thoroughly investigated.

As regards *targetry*, new ideas related to development of both target materials and target holders are emerging. New electrolytic procedures are being optimised to prepare suitable targets consisting of highly enriched expensive target isotopes, for example, ^{64}Ni to produce ^{64}Cu, ^{68}Zn to produce ^{68}Ga, ^{192}Os to produce ^{193m}Pt. In many other cases, new intermetallic compounds or alloys are being developed for use as target materials, for example, NiSe to produce ^{77}Br, WO_3, WC and WS_2 to produce^{186}Re. Ingenuity in designing and constructing target holders has been demonstrated, for example, solution targets for use at medical cyclotrons, vertical

targets for irradiating molten materials and tandem targets for full utilization of intermediate energy beams. Further efforts would continue also in the future.

With regard to *efficient chemical processing*, newer chelating agents are being developed for solvent extraction studies and new resins for ion-exchange chromatography. To a limited extent, some nanomaterials are being developed for use in column chromatography. The use of online mass separation in the isolation of a few special radionuclides from spallation products has also been demonstrated. It is a promising development.

As regards *quality assurance* of the radionuclide produced, besides the usual radionuclidic, radiochemical and chemical purity requirements, there is enhancing demand on the specific activity of the novel metallic radionuclides, especially because labelling of medically interesting small molecules with those radionuclides is extremely sensitive to inactive metallic impurities present in the separated radionuclide. An interesting example is ^{186}Re for which several experimental and theoretical efforts have been described to obtain high specific activity [80, 270, 274–276, 281].

In short, extensive efforts are presently being invested in several directions to develop radionuclide production technologies for the future.

7.3 New Directions in Radionuclide Applications

The use of radionuclides in medicine for diagnostic and therapeutic purposes is continuing and even enhancing. In addition, three new directions in applications are emerging (see [36] and Appendix VI):

- Theranostic approach
- Multimode imaging
- Radioactive nanoparticles

The *theranostic approach* entails a combination of diagnosis and internal radionuclide therapy. By combining a β^+ and a β^- (or Auger electron or α-particle) emitting pair of radionuclides of a given element in the same chemical form, it is possible to measure the uptake kinetics by PET imaging, thereby allowing an accurate dosimetric calculation related to therapy. This methodology of applying a *matched pair* of radionuclides on a specific patient is called *personalised medicine*. It was first applied in the case of internal therapy with ^{90}Y after mixing it with the positron emitter ^{86}Y [194]. Today, several other pairs are also finding great interest. They are ^{44g}Sc/^{47}Sc; ^{64}Cu/^{67}Cu; ^{83}Sr/^{89}Sr; ^{124}I/^{131}I; ^{152}Tb/^{161}Tb, ^{152}Tb/^{149}Tb. A very recent review discussed their production possibilities in detail [214]. Further development of those pairs as well as of a few other pairs is continuing.

The *multimode imaging* involves a combination of two or more organ-imaging techniques. The PET (and to some extent also SPECT) is being coupled with X-ray

tomography (CT) and magnetic resonance imaging (MRI). The latter combination is particularly interesting due to quantitative nature of PET and high resolution of MRI. In MRI, the elements Mn and Gd are often used as contrast agents. In the case of manganese, the positron emitting radionuclide ^{52}Mn has attracted considerable attention [177–180, 291], and authentic tracers labelled with ^{52}Mn have been prepared [292, 293]. As regards gadolinium, no positron emitting radionuclide is available. In that case, either SPECT utilizing ^{147}Gd [290] and MRI could be combined, or some other strategies could be followed (see Section 4.2 in Appendix VI).

The use of *radioactive nanoparticles* in medicine is presently under active investigation (see section 4.2 in Appendix VI). The expectation is to ensure a more effective delivery of the radionuclide, through the use of nanoparticles, to the organ or tissue under investigation. In animal studies, some limited applications of nanotargeted materials in imaging and therapy have been demonstrated [294, 295]. Regarding use in humans, two problems have to be overcome: (a) toxicity of the material, (b) possible loss of the advantage of molecular level investigation. The radionuclides needed will probably be the same as in present day internal radiotherapy. However, extensive further development work is needed to achieve the aim.

7.4 Future Perspectives of Medical Radionuclide Production

Development of radionuclide production technology is a thriving and dynamic field and is expected to lead to availability of a large number of novel radionuclides for use or potential use in newly emerging medicinal concepts, especially theranostics and multimode imaging. Very promising appears to be the realization among the scientists and technologists to contribute to human health by considering all channels and possibilities of radionuclide production, not only utilizing reactors and cyclotrons but also even exotic and purely research facilities, for example, heavy-ion accelerators and on-line mass separators associated with spallation machines. Those efforts could lead to availability of highly neutron-deficient radionuclides in the heavy mass region, of particular interest in PET studies and Auger therapy. On the other hand, it is emphasised that the clinical use of a radionuclide demands its availability in sufficient quantity, high purity and high specific activity. Thus reliance on reactors and low to intermediate energy accelerators will remain. Although all vistas should be kept open, in many cases concerted interdisciplinary efforts will be needed to reach the goals. Since the work involved is a blend of fundamental nuclear studies and technological development, it should be stimulating to young researchers as well. The perspectives of the field thus appear to be very bright.

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Appendices

Appendix I

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Nuclear Data Relevant to Cyclotron Produced Short-Lived Medical Radioisotopes

By S. M. Qaim, Institut für Chemie 1 (Nuklearchemie), Kernforschungsanlage Jülich GmbH, D-5170 Jülich, Federal Republic of Germany

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Short-lived radioisotope / In-vivo application / Nuclear data / Decay data / Cyclotron / Charged particle / Nuclear reaction / Cross section / Excitation function / Thick target yield

Summary

The choice of a radioisotope for medical applications demands an accurate knowledge of nuclear structure and decay data. The charged particle induced nuclear reaction cross section data, on the other hand, are needed for optimizing the production of a radioisotope, especially for calculating production yield and impurities as well as for target design and chemical processing. A short description of the experimental and calculational methods used in the determination of cross section data is given. The status of available nuclear data is reviewed. Whereas the decay data are generally well-known, new nuclear reaction cross section data are continuously needed to follow the newest trends in radiopharmaceutical design. Some of those needs are briefly outlined.

1. Introduction

The term nuclear data is very broad since almost any type of data originating from the decay of radioactive nuclei or from the interactions of nuclei with matter fall under this heading. However, as shown in Fig. 1, all the data can be generally grouped into two classes, *viz.*

1) Nuclear structure and decay data
2) Nuclear reaction data

From the viewpoint of fundamental nuclear chemistry and nuclear physics the data base in both the cases may be considered to be sufficiently extensive. From the user-oriented point of view as well the existing nuclear structure and decay data, as documented in various compilations [cf. 1–3], are extensive. Only in some special cases the branching ratios or γ-ray transition intensities are less certain. As far as application-oriented nuclear reaction data are concerned, the available information is extensive in some cases but scanty in others. In the case of neutron induced reactions, for example, the data base is strong. Most of the radioisotopes produced in nuclear reactors use one of the four methods, *viz.* (n, γ), (n, p), (n, α) and (n, fission). The cross sections for all pertinent reactions concerned are in general well-known [cf. 4]. In the case of charged particle induced reactions, on the other hand,

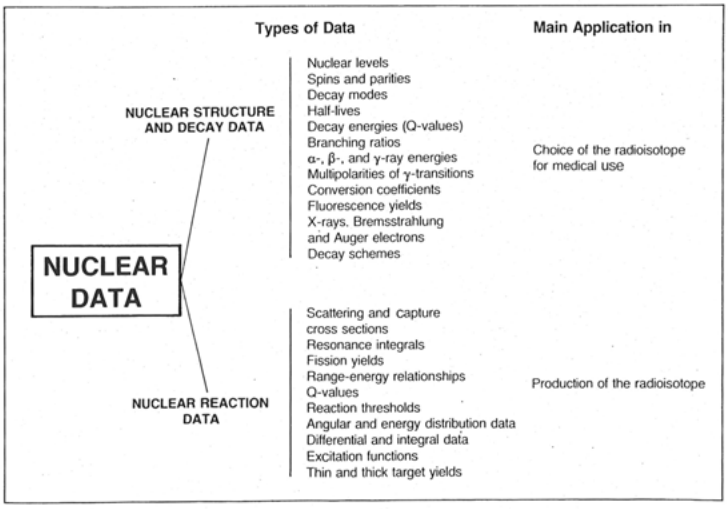

Fig. 1. Types of nuclear data and their main applications relevant to medical radioisotopes

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the integral cross section data needed for isotope production have received comparatively lesser attention. First efforts on the compilation of user-oriented charged particle data were started at Karlsruhe [5] and semi-empirical procedures were developed [6] for calculating unknown cross sections. Recently periodical bibliographies of integral charged particle nuclear data, dealing specifically with the problem area of isotope production, have been issued by the Nuclear Data Center at BNL [cf. 7].

First systematic and critical studies on the role and status of charged particle induced integral cross section data relevant to the production of short-lived radioisotopes using cyclotrons were initiated at Jülich [8, 9]. The matter was also discussed at a recent IAEA-Consultants' Meeting [10]. The present review deals with the subject in somewhat more detail. The aim is, however, not to give an exhaustive compilation of the data but to treat those salient features of nuclear data research which are of importance to medical radioisotope production programmes.

2. Importance of nuclear data

2.1. Nuclear structure and decay data

These data are needed for selecting a particular radioisotope for in-vivo medical applications. The selection is determined by two factors, namely

a) the resolution and efficiency of the radiation detecting system used, and
b) radiation dose caused to the patient.

Use of a conventional photon detecting camera requires an isotope with principal γ-ray energies in the range of 60 to 300 keV. Good quality scans can be obtained only if high-energy γ-rays are absent. This criterion limits the number of radioisotopes useful or potentially useful in diagnostic nuclear medicine to about 50. Similarly in positron emission tomography (PET) radioisotopes with strong β^+ branchings are needed. The energy of the positrons, however, is also important since high β^+ energies lead to long annihilation paths, affecting thereby the resolution of the detectors adversely. For example, of all the short-lived positron emitters used so far in nuclear medicine (^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{30}P, ^{75}Br) ^{18}F has the lowest positron end point energy (E_{β^+} = 0.635 MeV). From the viewpoint of decay data it is therefore the best positron emitting radionuclide for PET.

The radiation dose caused to the patient is a very important consideration in the choice of a radioisotope. The radioisotope should preferably not be a β^-- or α-emitter. Several methods are used to calculate specific organ or whole body doses. They assume various modes of distribution of the radionuclide in the body. The basic data needed for all the calculations, however, are the same [cf., e.g. 11]. In general terms, a knowledge of the decay scheme of the radioisotope is essential. In specific terms, information is needed on such parameters as half-life, the number of particles or photons emitted per disintegration as well as the mean energies of the particles and the photons. One of the main reasons for choosing short-lived radioisotopes for in-vivo investigations is the low radiation dose caused to the patient. The use of 13.02 h ^{123}I, instead of 8.04 d ^{131}I, in thyroid studies for example, can reduce the radiation dose to the patient by a factor of about 100 [12].

Despite the fact that nuclear structure and decay data are important in deciding which radioisotope would be potentially useful for medical applications, it should be emphasized that besides suitable nuclear properties, chemical and biochemical properties of the radioelement have also to be taken into account.

2.2. Nuclear reaction cross section data

These data are needed in connection with the production of radioisotopes. The data are important for

(i) determining the energy range optimum for the production of a specific radioisotope,
(ii) calculating the expected thick target yield of the isotope to be produced,
(iii) calculating the yields of radionuclidic impurities for a given thickness and enrichment of the target material.

A selection of the projectile energy range that will maximize the yield of the desired product and minimize that of the radioactive impurities is of vital importance in optimizing a production method. At low projectile energies the number of open reaction channels is generally small but with increasing incident particle energies several competing reactions set in. Whereas the non-isotopic impurities produced can be removed by chemical separations, the level of isotopic impurities can be suppressed only by using enriched isotopes as target materials and/or by a careful selection of the particle energy range effective at the target. The production of ^{123}I via the ^{124}Te(p, 2n)^{123}I reaction furnishes a good example for this. In order to decrease the level of isotopic impurities in the ^{123}I produced it is essential to use highly enriched ^{124}Te. However, due to the competing ^{124}Te(p, n)^{124}I reaction it is not possible to eliminate the ^{124}I impurity completely, even if ^{124}Te is 100% enriched. Fig. 2, based on the excitation function measurements by KONDO *et al.* [13], shows that the ideal proton energy range for the production of ^{123}I is E_p = 26.2 → 21.5 MeV, i.e. the energy of the incident protons should be selected as 26.2 MeV and the thickness of the tellurium target should degrade the incident energy only to 21.5 MeV. Under practical production conditions using compact cyclotrons (E_p = 22.4 → 20 MeV, ^{124}Te 99.97% enriched) it has been shown [cf. 14] that the level of undesired ^{124}I activity lies at 0.9%. Evidently in such special cases it is necessary to know the excitation functions of the various competing reactions accurately.

Though the use of a highly enriched target material may generally yield the desired radioisotope in a high radionuclidic purity, in cases where target technology is not sufficiently advanced use of another nuclear process on a different target element (of even natural isotopic composition) and a careful selection of the optimum energy may be of considerable advantage. For example, high-purity

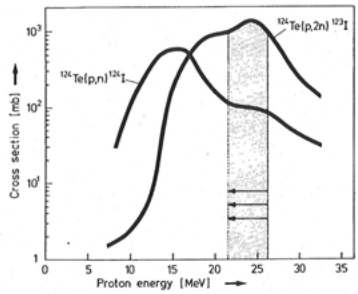

Fig. 2. Excitation functions of ^{124}Te(p, n)^{124}I and ^{124}Te(p, 2n) ^{123}I reactions. The optimum energy range for the production of ^{123}I is $E_p = 26.2 \rightarrow 21.5$ MeV [13]

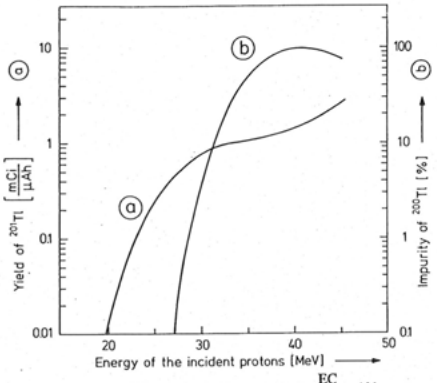

Fig. 3. (a) Yield of ^{201}Tl via ^{nat}Tl(p, xn)^{201}Pb $\xrightarrow[9.4\,h]{EC}$ ^{201}Tl as a function of the incident proton energy, (b) ^{200}Tl impurity as a % of ^{201}Tl activity at varying incident proton energies [16]

^{201}Tl can be produced via the ^{201}Hg(p, n)^{201}Tl reaction using highly enriched ^{201}Hg as target. However, since neither elemental mercury nor any of its known compounds are capable of withstanding high currents, the preferred route of production of ^{201}Tl is via the ^{203,205}Tl (p, xn)^{201}Pb $\xrightarrow[9.4\,h]{(EC)}$ ^{201}Tl-process. The limiting factor in this process is the impurity level of ^{200}Tl. Excitation function measurements [cf. 15, 16] revealed that the optimum incident proton energy is 28 MeV. Fig. 3 shows that at 28 MeV the undesired ^{200}Tl-impurity is $< 1\%$. At higher energies the ^{201}Tl-yields are significantly higher but it is also true for the ^{200}Tl-contamination.

As mentioned above, at high incident particle energies several competing reactions occur. With the increasing projectile energies the data needs, therefore, also increase. An example is furnished by our recent investigations [17, 18] on the production of ^{77}Br and ^{75}Br via their krypton precursors. Fig. 4(A) shows the excitation functions for the formation of ^{77}Kr, ^{76}Kr and ^{75}Kr via the ^{79,81}Br(d, xn)-processes over the incident deuteron energy range of 20 to 90 MeV. Using those data it was found that the optimum deuteron energy range for the production of ^{75}Br via its precursor is 90 → 68 MeV (Fig. 4(B)). The contamination of ^{75}Kr from ^{77}Kr is apparently high. However, by a careful selection of the growth (and decay) time of ^{75}Kr the contamination of ^{75}Br from ^{77}Br can be reduced to $< 6\%$ [18].

The production of radioactive rare gases like $^{75-77}$Kr with incident particle energies exceeding 50 MeV constitutes a rather special case because of the ease of chemical separation. In most of the other cases, however, extensive chemical processing is necessary [cf. 19, 20]. A knowledge of the nuclear data helps in estimating the total activity [cf. 20, 21]. As an example, Fig. 5 shows the yields of various radioisotopes formed as a function of incident ^{3}He-particle energy on titanium [20]. There is no energy region where the desired ^{48}Cr activity is formed preferably. An elaborate chemical separation is therefore most essential [20].

A knowledge of the excitation function also plays an important role in designing gas targets. The incident energy of the projectiles, the length of the target as well as the pressure of the target gas are to be selected in such a way that only the desired portion of the excitation function is utilized, the remaining energy of the projectiles being dumped on a beam-stop. A gas target system for the production of ^{11}C via the ^{14}N(p, α)^{11}C reaction is shown in Fig. 6. The cross section data used in the design calculations were taken from the work of JACOBS *et al.* [22] and

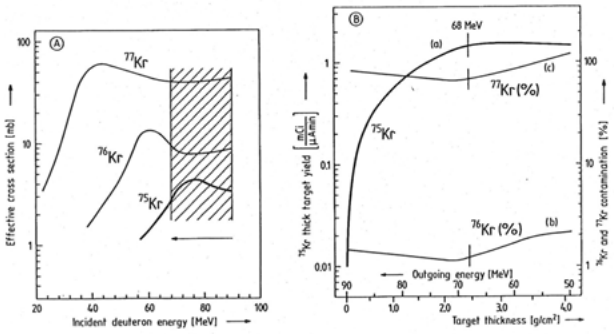

Fig. 4. (A) Excitation functions for the formation of ^{77}Kr, ^{76}Kr and ^{75}Kr in deuteron induced nuclear reactions on natural bromine [17, 18], (B) Determination of the optimum energy region for the production of ^{75}Kr: (a) Thick target yield of ^{75}Kr, (b) and (c) contamination of ^{75}Kr by ^{76}Kr and ^{77}Kr, respectively, plotted against natural bromine target thickness at a constant incident deuteron energy of 90 MeV. The optimum energy range is $E_d = 90 \rightarrow 68$ MeV [18]

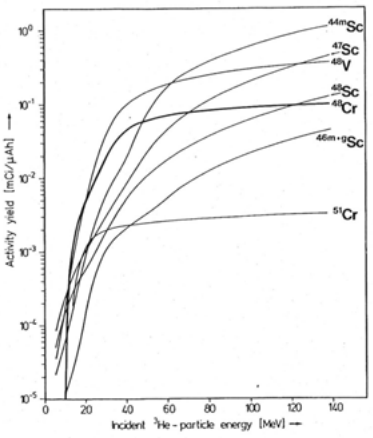

Fig. 5. Thick target yields of ^{48}Cr and the major impurities as a function of incident ^{3}He-particle energy on titanium [20]

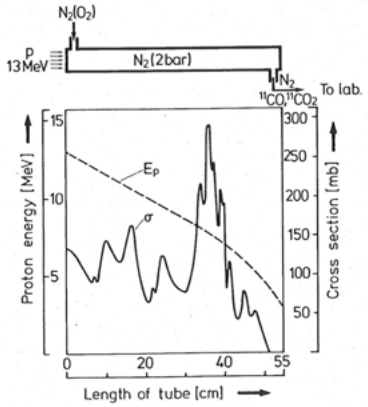

Fig. 6. Schematic diagram of target and irradiation conditions for the production of ^{11}C via the reaction ^{14}N (p, α)^{11}C. The cross section [22, 23] and the absorption of the protons in the target are shown as a function of the target length

CASELLA *et al.* [23]. Since ^{11}C is the only radioisotope of carbon formed, the full range of the excitation function can be used. Designing a target without a knowledge of the excitation function may lead to the use of excessive gas.

The yield of a radioisotope expected from a particular thickness of the target (thick target yield) can be calculated by an integration of the measured excitation function over the energy range covered by the target, using the relation

$$Y = \frac{N_L \cdot H}{M} I(1 - e^{-\lambda t}) \int_{E_1}^{E_2} \left(\frac{dE}{d(\rho x)}\right)^{-1} \sigma(E)\, dE$$

where N_L is the Avogadro number, H the enrichment (or isotopic abundance) of the target nuclide, M the mass number of the target element, I the projectile current, $\left(\frac{dE}{d(\rho x)}\right)$ the stopping power, $\sigma(E)$ the cross section at energy E, λ the decay constant of the product and t the time of irradiation.

The calculated yield value represents the maximum yield which can be expected for a given target system. In practice, however, the experimentally obtained yields in high-current production runs are invariably lower than the theoretical values, possibly due to inhomogeneity in the incident beam, radiation damage effects, loss of the product as a result of high power density effective at the target, etc.

Occasionally some users tend to believe that full information on the excitation function of the nuclear reaction applied for the production of an isotope is not necessary and that only experimental thick target yield data are sufficient. This approach may be more practical but it remains empirical since the basic parameter in the production of an isotope is the cross section and *not* a particular target yield. The latter reflects only the specific conditions prevalent during the production process. An accurate knowledge of the excitation function, and therefrom the theoretical thick target yield, helps in designing target systems capable of giving higher yields. It should, however, be emphasized that the problems associated with the large scale production of radioisotopes are not solved simply by measuring the cross sections. Other factors like suitability of materials for target construction, heat transfer, remote handling, chemical processing and quality control, etc. are often of greater importance. It is therefore imperative that efforts in the field of nuclear data should go hand in hand with the other development work.

Similar to the yield calculation for the desired radioisotope, the yields of the impurities can also be calculated if the excitation functions of the competing reactions are known. It is then easy to keep a check on the radionuclidic impurities associated with a particular production method.

3. Experimental methods in the determination of nuclear reaction cross section data

The available information on nuclear structure and decay data as well as on neutron induced reactions is extensive; no discussion is given here.

Since in the case of charged particle induced reactions investigations are generally carried out to study nuclear reaction theories, the main emphasis in those investigations lies on the measurement of emitted particles, especially their energy and angular distributions. In principle an integration of the emitted particle spectrum over the whole range of energy and angular distribution would yield the cross section for the formation of a product nucleus. In practice, however, such fundamental studies on nuclear reactions hardly report integrated cross sections for the formation of product nuclei. Though some attempts to determine the formation cross sections of the medically important radioisotopes ^{11}C, ^{13}N and ^{18}F via measurements of the neutron spectra emitted in (p, n) reactions

on ^{11}B, ^{13}C and ^{18}O, respectively, have been fairly successful [cf. 24], the integral cross section data as a function of incident particle energy (excitation functions), needed in isotope production, have been almost exclusively measured by the user himself, often utilizing radiochemical techniques. We discuss some important features of those measurements below.

Two techniques are commonly used for measuring excitation functions. The first one is applicable in the case of variable energy cyclotrons. Thin samples of the target material are irradiated either with extracted beams of varying energies or at appropriate radii in the internal beam [cf. 25]. The activated products are assayed quantitatively via radiochemical methods. The second technique consists of irradiating a set of foils or pellets in a stack and determining the activity in each foil. The incident particle beam loses energy on passing through the stack so that a different energy is effective at each foil. This technique is called "stacked-foil" or "stacked-pellet" technique. Besides foils and pellets the technique has also been applied in the case of gas targets [cf. 26–28]. Several thin walled gas cylinders are placed in a row to constitute a stack of samples.

The stacked foil, pellet or cylinder technique is very useful since cross section data at several energies are obtained in a single irradiation. On the other hand, if proper precautions are not taken, considerable errors both in the energy scale and the cross section may occur. Since this technique is more commonly used in cross section work relevant to radioisotope production, we discuss some of its salient features in more detail.

3.1. Sample preparation

In order to obtain a large number of cross section data points over a given energy range and with a view to avoiding excessive energy degradation in each foil it is essential to use thin foils. This is all the more important in the low-energy rising part of the excitation curve to be able to get more detail. The foils should, however, be thick enough to produce measurable activities for getting good counting statistics. In the case of ductile metals (e.g. Al, Ti, Cu, Mo, Ag, Au etc.) foils of varying thicknesses are commercially available. Thin foils of non-metallic and amorphous substances, however, are difficult to get and often special preparative methods are necessary. In the case of powdery substances like NaI, NaBr and CsCl, for example, thin pellets were obtained by pressing the powder at a pressure of 2.5 t/cm^2 [cf. 17, 29–31]. Similarly in the case of sulphur, conversion of ordinary sulphur to plastic sulphur followed by pressing [32] on to a Ti-foil gave a thin pellet. The techniques of sublimation and vacuum evaporation have also been used for getting thin films on a suitable backing [cf. 33]. Uniform suspension of the target material in a self-supporting polystyrene film has found some application [cf. 13, 34]. Sometimes electrolytic deposition is successfully applied [cf., e.g. 35] which gives rise to desirably thin films that are uniform in thickness, dense and adherent. Uniformity in the thickness of the film is a very important parameter in cross section work.

In addition to the thickness of the foil it is important to keep a check on the chemical purity of the material. Furthermore, if an enriched isotope is used as target material it is important to know not only the percentage enrichment of the target isotope but also the exact isotopic composition of the target since many of the radioactive impurities accompanying the desired radioisotope may originate via nuclear reactions on the less abundant isotopes in the target.

3.2. Radiochemical separations

In many cases the radioactive product under investigation may be determined quantitatively via high-resolution γ-ray spectroscopy without involving a radiochemical separation. For identification of low-yield products or for products emitting soft radiation (e.g. ^{125}I) it is, however, almost invariably necessary to isolate the desired radioisotope from the matrix activity. Methods like adsorption, precipitation, ion-exchange chromatography, high-pressure liquid chromatography, solvent extraction, dry as well as wet distillation, etc. have been commonly employed.

3.3. Counting methods

Most of the radioisotopes potentially useful for in-vivo applications emit suitable γ-rays. In cross section work therefore high-resolution γ-ray spectroscopy is commonly employed. In the case of β^+ emitters, on the other hand, if no characteristic γ-ray is emitted (e.g. ^{18}F, ^{30}P), use is generally made of the 511 keV annihilation radiation, either via γ-ray spectroscopy or via $\gamma\gamma$-coincidence counting. However, since annihilation radiation is emitted by every β^+ emitter, it is absolutely necessary to carry out a full analysis of the decay curve. If two β^+ emitters of almost similar half-lives are expected, a β-spectrometric analysis is essential. In a recent work on ^{30}P ($T_{1/2}$ = 2.5 min), for example, it was suspected that some ^{15}O ($T_{1/2}$ = 2.0 min) may be present. Measurement of $\beta^+ > 2.0$ MeV (i.e. beyond the cut-off energy of the positrons from ^{15}O) therefore yielded accurate contributions of ^{30}P [32].

3.4. Beam current monitoring

One of the most important parameters in the determination of a cross section is the measurement of the beam current incident on each foil. Two methods are generally applied for this purpose. In the first method which is applicable in the case of thin stacks, the outgoing beam falls in a Faraday cup and the total charge collected is registered. In order to avoid some possible errors due to secondary electrons produced, WATSON *et al.* [36] suggested the use of a "spinning wheel" (containing several stacks of samples) and a calorimetric beam integration system. The method has, however, found limited application. In the second

method use is made of a monitor reaction whose excitation function is known accurately. For this purpose several foils of the monitor target material are inserted at several places in the stack. This method is applicable even in the case of thick stacks, i.e. when the whole beam is stopped in the stack. It is, however, recommended that whenever possible both a Faraday cup and a monitor foil be used for beam current measurements.

3.5. Excitation functions and their errors

From the measured radioactivity in each foil and the effective beam current the cross section is obtained using the well-known activation equation. The energy of the incident particle effective at each foil is obtained using the stopping powers of various materials [cf. 37, 38]. A plot of the cross section against the respective energy thus yields the excitation function needed in isotope production work.

There are three major sources of uncertainty in the measured excitation functions:

(i) Determination of beam current
(ii) Determination of absolute activity of the activation product
(iii) Range-energy calculations.

Beam current measurements using a Faraday cup are generally more accurate. In many of the excitation functions reported so far, however, use has been made of monitor reactions for measuring beam currents. Though many monitor reactions have been suggested, unfortunately, as yet there are no agreed sets of standards [cf. 10], so that a critical evaluation of the reported cross section data is often difficult.

The uncertainty in the determination of the absolute activity of the activation product arises mainly from the uncertainty in the efficiency of the counting system as well as the decay data used. In most cases both the efficiency and the decay data are known well so that in general the total error due to this source does not exceed 3%. In some special cases, however, uncertainties in the decay data, and therefore in the cross sections, may be appreciable.

The uncertainties in range-energy calculations lead to errors in the energy scale. Use of rather thick foils in the case of low energy projectiles leads to considerable errors, and in the sharply increasing or decreasing section of an excitation function may mask the fine structure, if any.

The cross section data reported have in general errors of about 10 to 15%; for low-yield products the total errors may be up to 25%.

4. Calculational methods for determining nuclear data

Nuclear theory and systematics are sufficiently advanced to predict nuclear structure and decay data for normal nuclei with reasonable accuracies. Only for light nuclei and for those far away from the stability line the predictions are less certain.

As far as the cross section data for nuclear reactions induced by neutrons are concerned, elaborate formalisms and detailed methods of calculation have been reported. The theory of radiative capture, for example, has been well worked out. The (n, p) and (n, α) reaction cross sections, up to incident neutron energies of 10 MeV, can be calculated by the HAUSER-FESHBACH theory, and the fission yields can be well predicted from the systematics.

Although extensive theoretical studies on nuclear reactions induced by charged particles have also been carried out, there is still considerable need for developing further calculational methods to deliver user-oriented cross section data. It is known that both the systematics and calculational methods have strong uncertainties in the case of light mass nuclei, a region of vital importance in the life sciences. Furthermore, since with the increasing energies of the incident particles the number of competing reactions increases, rather extensive calculational methods are necessary to describe the excitation functions, especially in the energy region beyond 30 MeV.

A general method for calculating reaction cross sections up to excitation energies of about 200 MeV consists of using the statistical model but incorporating precompound emission of particles via the hybrid model. The results for $^{nat}Br(p, xn)^{76,77}Kr$ and $^{nat}Tl(p, xn)^{201}Pb$, calculated by NOWOTNY [39, 40] using the code ALICE, are shown in Fig. 7 and compared with the available experimental data. It appears that the calculational method can reproduce an excitation function fairly well in the heavy mass region but only with greater uncertainties in the medium mass region [cf. also 41, 42]. Despite the fact that such calculations can hardly reproduce excitation functions universally, they appear to be useful for approximate estimations of proton-induced production yields.

Somewhat similar calculations for deuteron induced reactions on heavy mass nuclei have also been quite successful [43]. In the medium mass region, however, the discrepancy between the experimental data and calculated values is much more than that in the case of proton induced reactions [40]. Cross sections of nuclear reactions induced by complex particles like ^3He and ^4He are even more difficult to calculate and are associated with higher uncertainties

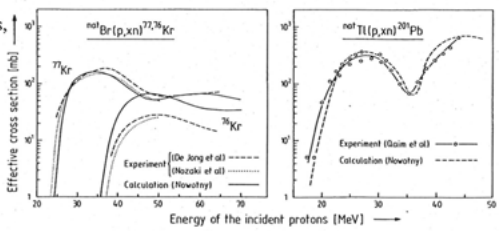

Fig. 7. Comparison of experimental and theoretical excitation functions for the formation of ^{77}Kr and ^{76}Kr via p-induced nuclear reactions on ^{nat}Br, and of ^{201}Pb via p-induced reactions on ^{nat}Tl [40]

[cf. 44]. Though the excitation functions of such reactions in the heavier mass region have been reproduced with some success, a general use of the calculational method for obtaining application-oriented data has so far not been attempted.

At energies above 200 MeV only the proton induced reactions have been used to some extent for isotope production, mainly at 600 and 800 MeV. Monte-Carlo type cascade-evaporation calculations are generally performed to estimate cross sections for the production of a large number of isotopes. Those calculations reproduce the cross sections generally better than a factor of 2.

4. Status of available nuclear data

All the radioisotopes used for in-vivo studies can be arbitrarily divided [cf. 8] into five groups (cf. Fig. 8) according to their chemical behaviour, biological function or mode of formation. The "organic" short-lived β^+ emitters are ideally suited for labelling biomolecules and find applications in positron emission tomography. Radiohalogens may also be regarded as "organic" isotopes since they are also useful for labelling biomolecules; some of them are suitable for in-vivo studies using conventional γ-cameras while the others find applications in positron emission coincidence tomography. Rare gases are generally used for ventilation studies. Since many of the radiohalogens are formed via rare gas precursors, these two types of radioisotopes are grouped together. Short-lived generator radionuclides are practical for general medical use since an on-site or nearby cyclotron is not required. Alkali and alkali like metals find applications in myocardial perfusion studies. The list of inorganic radionuclides is large but their applications are rather limited. A review of their production methods is given by WATERS and SILVESTER [45].

TYPES OF RADIONUCLIDES FOR IN-VIVO STUDIES

1. "ORGANIC" Short-lived β^+ emitters
   (^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{30}P etc.)
2. HALOGENS and RARE GASES
   (^{18}F, ^{34m}Cl, ^{75,77}Br, ^{123}I, ^{77,79,81m}Kr, ^{125}Xe etc.)
3. GENERATOR isotopes
   (^{68}Ge-^{68}Ga, ^{81}Rb-^{81m}Kr, ^{99}Mo-^{99m}Tc etc.)
4. ALKALI and alkali like metals
   (^{38,43}K, ^{81}Rb, ^{128,129}Cs, ^{201}Tl etc.)
5. "INORGANIC" radionuclides
   (^{28}Mg, ^{45}Ti, ^{48}Cr, ^{73}Se, ^{97}Ru etc.)

Fig. 8. Types of radionuclides used for in-vivo medical applications

Each radioisotope can be generally produced via several nuclear reactions. Not every reaction, however, is suitable for large scale production of a particular isotope. Apart from cross section data, such considerations as ease of target construction, capability of withstanding high beam currents as well as the subsequent chemical processing have to be taken into account. Our recent investigations on the production of 2.5 min ^{30}P [32, 46] constitute a somewhat typical example. This isotope can be produced in a carrier-free form via four processes, *viz.* ^{27}Al(α, n)^{30}P, ^{32}S(d, α)^{30}P, ^{28}Si(^{3}He, p)^{30}P and ^{28}Si(α, d)^{30}P. A consideration of the various factors involved, however, showed that the ^{27}Al(α, n)^{30}P reaction is the most suitable.

Out of the various projectiles applicable for the production of a radioisotope, the use of high energy bremsstrahlung, for example through processes like (γ, xp) and (γ, xn) is rather limited [cf. 47, 48] since the cross sections are low. Similarly heavy-ion induced reactions also give rather low-yields [cf. 49, 50]. In practice one is therefore generally limited to the use of one or more of the four projectiles p, d, ^{3}He and ^{4}He. For compound nucleus type reactions in the medium and heavy mass regions the yields are generally highest while using protons. In recent years, however, ^{3}He-particles have found increasing applications since the energies of ^{3}He^{2+}-particles available at compact cyclotrons are generally higher than those of other particles. Thus, several of the newer methods of production of ^{48}Cr, ^{75}Br, ^{77}Kr, ^{97}Ru etc. make use of ^{3}He^{2+}-particles. As an example, the data for the production of ^{94,95,97}Ru are reproduced in Fig. 9. Since molybdenum of natural isotopic composition was used as target material, the excitation functions are rather complex. In comparison to the α-particle induced production, the ^{3}He-method has the advantage that the longer-lived ^{103}Ru is not formed [51].

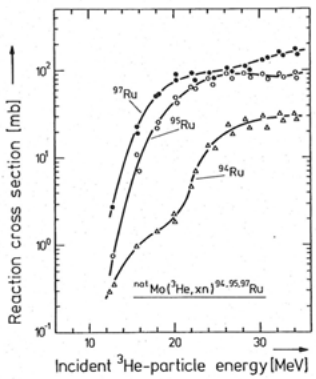

Fig. 9. Excitation functions for the formation of ^{94}Ru, ^{95}Ru and ^{97}Ru in the interactions of ^{3}He-particles with natural molybdenum [51]

Table 1 summarizes the decay and production data for some medically useful short-lived cyclotron radioisotopes in the ascending order of Z. As mentioned above the nuclear structure and decay data are generally well-known and have been taken from Refs. 1 and 2. Those cases where uncertainties in data exist are pointed out. The major nuclear reactions useful or potentially useful for production

Table 1. *Nuclear data relevant to the production and medical application of some important cyclotron produced short-lived radioisotopes*

Radioisotope	Decay data				Nuclear reaction cross section data			
	Half-life	Mode of decay (%)	End point energy of β groups keV (rel. %)	Principal γ-rays keV (% abundance)	Principal nuclear reactions	Energy range (MeV)	Major references	Status
^{11}C	20.3 min	β^+ (99.8), EC (0.2)	960 (100)	511 (199.6)	$^{14}N(p, \alpha)^{11}C$	$15 \rightarrow 4$	5, 22, 23, 52	good
					$^{11}B(p, n)^{11}C$	$20 \rightarrow 3$	5, 24	fair
					$^{10}B(d, n)^{11}C$	$10 \rightarrow 0$	5	fair
					^{12}C p, pn)^{11}C	$45 \rightarrow 10$	5	good
					$^{12}C(^3He, ^4He)^{11}C$	$30 \rightarrow 0$	5	fair
^{13}N	9.96 min	β^+ (100)	1190 (100)	511 (200)	$^{12}C(d, n)^{13}N$	$15 \rightarrow 0$	5	fair
					$^{13}C(p, n)^{13}N$	$12 \rightarrow 0$	24	fair
					$^{16}O(p, \alpha)^{13}N$	$20 \rightarrow 5$	5	fair
^{15}O	2.03 min	β^+ (99.9), EC (0.1)	1723 (100)	511 (199.8)	$^{14}N(d, n)^{15}O$	$6 \rightarrow 0$	5, 53	good
					$^{12}C(\alpha, n)^{15}O$			
^{18}F	109.7 min	β^+ (96.9), EC (3.1)	635 (100)	511 (193.8)	$^{16}O(^3He, p)^{18}F$	$40 \rightarrow 0$	5, 26, 54	good
					$^{16}O(\alpha, d)^{18}F$	$20 \rightarrow 0$	5	fair
					$^{20}Ne(d, \alpha)^{18}F$	$30 \rightarrow 0$	26, 28	good
					$^{18}O(p, n)^{18}F$	$15 \rightarrow 3$	24, 55	fair
					$^{20}Ne(d, x)^{18}Ne$ $^{18}Ne \xrightarrow[1.7s]{\beta^+} {}^{18}F$	$80 \rightarrow 35$	28	good
					$^{20}Ne(^3He, \alpha n)^{18}Ne$ $^{18}Ne \xrightarrow[1.7s]{\beta^+} {}^{18}F$	$32 \rightarrow 18$	28	good
					$^{16}O(^3He, n)^{18}Ne$ $^{18}Ne \xrightarrow[1.7s]{\beta^+} {}^{18}F$			
^{28}Mg	21.1 h	β^- (100)	460 (100)	401 (35.9), 942 (35.9), 1342 (54.0)	$^{26}Mg(t, p)^{28}Mg$	$20 \rightarrow 2$	56	fair
					$^{27}Al(t, 2p)^{28}Mg$	$20 \rightarrow 4$	56	fair
					$^{26}Mg(\alpha, 2p)^{28}Mg$	$140 \rightarrow 15$	5, 21	good
					$^{27}Al(\alpha, 3p)^{28}Mg$	$140 \rightarrow 30$	5, 21	good
					$^{30}Si(\gamma, 2p)^{28}Mg$	$e^- 60 \rightarrow 30$	57	fair
					Si, P, S Cl, Ar, K $\}$ (p, x)^{28}Mg	$180 \rightarrow 50$	58	good
^{30}P	2.5 min	β^+ (100)	3245 (100)	511 (200)	$^{31}P(p, pn)^{30}P$	$35 \rightarrow 18$	46	good
					$^{27}Al(\alpha, n)^{30}P$	$28 \rightarrow 10$	46	good
					$^{28}Si(^3He, p)^{30}P$	$36 \rightarrow 12$	32	good
					$^{28}Si(\alpha, d)^{30}P$	$28 \rightarrow 16$	32	fair
					$^{32}S(d, \alpha)^{30}P$	$14 \rightarrow 4$	32	good
^{38}S	2.8 h	β^- (100)	1005 (95), 3000 (5)	1942 (84.0)	$^{40}Ar(p, 3p)^{38}S$	$50 \rightarrow 30$	60	good
					$^{40}Ar(\gamma, 2p)^{38}S$	$e^- 85 \rightarrow 60$	47, 59	fair
^{34m}Cl	32.0 min	β^+ (53.0), IT (47.0)	1350 (43), 2470 (57)	146 (42), 511 (106), 1176 (13.5) 2127 (42)	$^{35}Cl(p, pn)^{34m}Cl$	$45 \rightarrow 10$	61	fair
					$^{32}S(^3He, p)^{34m}Cl$	$30 \rightarrow 5$	62, 63	fair
					$^{31}P(\alpha, n)^{34m}Cl$	$42 \rightarrow 10$	63	poor
^{38}K	7.6 min	β^+ (100)	2600 (100)	511 (200), 2167 (99.8)	$^{40}Ar(p, 3n)^{38}K$	$32 \rightarrow 30$	64	poor
					$^{40}Ca(d, \alpha)^{38}K$	$5 \rightarrow 2$	5	fair
					$^{35}Cl(\alpha, n)^{38}K$	$30 \rightarrow 4$	65, 66	poor
					$^{37}Cl(\alpha, 3n)^{38}K$			
					$^{37}Cl(^3He, 2n)^{38}K$	$20 \rightarrow 7$	62	fair
					$^{40}Ca(\gamma, pn)^{38}K$	$e^- 60 \rightarrow 30$	48	fair
					$^{40}Ca(^3He, \alpha p)^{38}K$	$20 \rightarrow 8$	62	fair
^{43}K	22.2 h	β^- (100)	460 (5.7), 827 (87), 1218 (5.7), 1839 (1.7)	373 (70), 618 (80)	$^{40}Ar(\alpha, p)^{43}K$	$35 \rightarrow 12$	5	fair
					$V(d, x)^{43}K$	$90 \rightarrow 45$	67	fair
					$V(p, spall)^{43}K$	590, 800	68	fair
^{47}Sc	3.42 d	β^- (100)	439 (68.5) 610 (31.5)	159 (68.5)	$^{48}Ti(\gamma, p)^{47}Sc$	$e^- 60 \rightarrow 30$	69	fair
					$^{51}V(\gamma, \alpha)^{47}Sc$	$e^- 60 \rightarrow 30$	69	fair
					$^{nat}Ti(d, x)^{47}Ca$ $^{47}Ca \xrightarrow[4.5d]{\beta^-} {}^{47}Sc$	$90 \rightarrow 40$	67	fair
					$Ni(p, spall)^{47}Sc$	800	68	fair

Table 1. Continued

Radioisotope	Decay data				Nuclear reaction cross section data			
	Half-life	Mode of decay (%)	End point energy of β groups keV (rel. %)	Principal γ-rays keV (% abundance)	Principal nuclear reactions	Energy range (MeV)	Major references	Status
^{45}Ti	3.08 h	β^+ (86), EC (14)	1044 (100)	511 (172), 720 (0.15)	^{45}Sc(p, n)^{45}Ti ^{45}Sc(d, 2n)^{45}Ti ^{44}Ca(^{3}He, 2n)^{45}Ti	14 → 3	5, 70	fair
^{48}Cr	21.6 h	EC (100)		112 (96), 308 (99.5)	^{51}V(d, 5n)^{48}Cr ^{nat}Ti(^{3}He, xn)^{48}Cr ^{nat}Ti(α, xn)^{48}Cr	90 → 45 130 → 10 170 → 20	20 20 20	good good good
^{51}Cr	27.7 d	EC (100)		320 (10.2)	^{51}V(p, n)^{51}Cr ^{51}V(d, 2n)^{51}Cr ^{nat}Ti(^{3}He, xn)^{51}Cr ^{nat}Ti(α, xn)^{51}Cr	40 → 0 90 → 5 130 → 10 170 → 10	5 20 20 20	good good good good
^{51}Mn	46.2 min	β^+ (97), EC (3)*	2210 (100)	511 (194)	^{50}Cr(d, n)^{51}Mn ^{52}Cr(p, 2n)^{51}Mn ^{51}V(^{3}He, 3n)^{51}Mn	12 → 3	5, 71	fair
^{52m}Mn	21.1 min	β^+ + EC (98.25)*, IT (1.75)	2631 (100)	511 (197.5), 1434 (98.2)	^{52}Cr(p, n)^{52m}Mn ^{52}Cr(d, 2n)^{52m}Mn ^{51}V(^{3}He, 2n)^{52m}Mn	16 → 6 18 → 5	71 71	poor poor
^{52}Mn	5.6 d	β^+ (27.9), EC (72.1)	575 (100)	511 (55.8), 744 (90), 936 (94.5), 1434 (100)	^{52}Cr(p, n)^{52}Mn ^{52}Cr(d, 2n)^{52}Mn ^{51}V(^{3}He, 2n)^{52}Mn	16 → 6 20 → 7 14 → 10	5 5 72	fair fair poor
^{52}Fe	8.3 h	β^+ (56.5), EC (43.5)	804 (100)	169 (99.2), 511 (113)	^{nat}Cr(α, xn)^{52}Fe ^{nat}Cr(^{3}He, xn)^{52}Fe Ni(p, spall)^{52}Fe	90 → 20 45 → 10 800	73, 74 73 68	fair fair fair
^{55}Co	18.0 h	β^+ (77), EC (23)*	550 (2.5), 1040 (41), 1500 (56.5)	477 (20.3), 511 (154), 931 (75), 1409 (16.5)	^{54}Fe(d, n)^{55}Co ^{56}Fe(p, 2n)^{55}Co ^{nat}Fe(^{3}He, x)^{55}Co ^{55}Mn(^{3}He, 3n)^{55}Co ^{55}Mn(α, 4n)^{55}Co	15 → 4 40 → 15 25 → 0 40 → 10	75 76 77 78	fair fair poor good
^{56}Ni	6.1 d	EC (100)		158 (98.8), 269 (35.6), 480 (35.6), 750 (49.4), 812 (87.4)	^{54}Fe(α, 2n)^{56}Ni ^{56}Fe(^{3}He, 3n)^{56}Ni	40 → 17 29 → 20	5 5	good fair
^{57}Ni	36.0 h	β^+ (40), EC (60)	350 (2.3), 712 (11.4), 850 (86.3)	127 (15.5), 511 (80), 1378 (77.6), 1919 (13.2)	^{54}Fe(α, n)^{56}Ni ^{56}Fe(^{3}He, 2n)^{56}Ni	40 → 6 29 → 6	5 5	good good
^{61}Cu	3.4 h	β^+ (62), EC (38)	560 (5), 940 (9), 1205 (86)	67 (6.9), 283 (13.2), 511 (124), 656 (11.7), 1186 (4.9)	^{60}Ni(d, n)^{61}Cu ^{nat}Ni(α, x)^{61}Cu ^{59}Co(α, 2n)^{61}Cu ^{75}As(p, spall)^{61}Cu	12 → 4 40 → 10 39 → 18 800	5 79 5 68	fair fair fair fair
^{62}Zn ↓ generator ↓ ^{62}Cu	9.1 h 9.7 min	β^+ (6.9), EC (93.1) β^+ (97.8), EC (2.2)	660 (100) 2930 (100)	507 (13.9), 511 (13.8), 548 (14.6), 597 (24) 511 (195.6), 1173 (0.36)	^{63}Cu(p, 2n)^{62}Zn ^{60}Ni(α, 2n)^{62}Zn ^{60}Ni(^{3}He, n)^{62}Zn ^{nat}Zn(γ, xn)^{62}Zn	100 → 15 38 → 12 23 → 0 e^- 60 → 30	5 5, 80 81 82	fair fair poor poor
^{67}Ga	78.3 h	EC (100)		93 (38), 185 (23.6), 300 (19)	^{66}Zn(d, n)^{67}Ga ^{67}Zn(p, n)^{67}Ga ^{68}Zn(p, 2n)^{67}Ga ^{nat}Zn(α, x)^{67}Ga ^{65}Cu(^{3}He, n)^{67}Ga ^{65}Cu(α, 2n)^{67}Ga As, Rb, Br(p, spall)^{67}Ga	15 → 2 6 → 2 85 → 15 40 → 10 70 → 10 40 → 10 800	5 5 83 84 5 5 68	fair poor fair fair good good fair

Table 1. Continued

Radioisotope	Decay data				Nuclear reaction cross section data			
	Half-life	Mode of decay (%)	End point energy of β groups keV (rel. %)	Principal γ-rays keV (% abundance)	Principal nuclear reactions	Energy range (MeV)	Major references	Status
^{68}Ge	288 d	EC (100)			^{69}Ga(p, 2n)^{68}Ge	55 → 13	5	good
↓ generator					^{71}Ga(p, 4n)^{68}Ge	56 → 36	5	good
					^{66}Zn(^{3}He, n)^{68}Ge			
					^{66}Zn(α, 2n)^{68}Ge			
					^{68}Zn(α, 4n)^{68}Ge			
^{68}Ga	68.3 min	β^+ (90), EC (10)	770 (1.7), 1900 (98.3)	511 (180), 1077 (3)				
^{73}Se	7.1 h	β^+ (65), EC (35)*	800 (8), 1320 (91.3), 1680 (0.7)	67 (71), 511 (130), 361 (97)	^{75}As(p, 3n)^{73}Se	50 → 25	85	good
					^{72}Ge(^{3}He, 2n)^{73}Se	37 → 17	34	good
					^{73}Ge(^{3}He, 3n)^{73}Se	36 → 31	34	fair
					^{70}Ge(α, n)^{73}Se	32 → 12	34	good
					^{73}Ge(α, 3n)^{73}Se	40 → 33	34	fair
					^{nat}Ge(^{3}He, x)^{73}Se	40 → 10	85	fair
					^{nat}Ge(α, x)^{73}Se	40 → 10	85	fair
^{75}Br	1.6 h	β^+ (75.5), EC (24.5)*	1130 (2), 1340 (7), 1450 (2), 1510 (7), 1740 (82)	286 (91.6), 511 (151)	^{76}Se(p, 2n)^{75}Br	34 → 16	86	good
					^{76}Se(d, 3n)^{75}Br	45 → 20	86	good
					^{75}As(^{3}He, 3n)^{75}Br	100 → 15	86, 87, 88	good
					^{75}As(α, 4n)^{75}Br	100 → 40	86, 87, 88	good
^{75}Kr	4.5 min	β^+ (75), EC (25)*	3200 (100)	132 (75), 154 (28)**	^{79,81}Br(d, xn)^{75}Kr	86 → 60	18	fair
					^{79,81}Br(p, xn)^{75}Kr			
↓ ^{75}Br	see above							
^{77}Br	57 h	β^+ (0.7), EC (99.3)	340 (100)	239 (22.8), 297 (4.1), 521 (22.1)	^{77}Se(p, n)^{77}Br	25 → 3	5	fair
					^{78}Se(p, 2n)^{77}Br	24 → 14	89	fair
					^{nat}Se(p, x)^{77}Br	50 → 5	90	fair
					^{75}As(α, 2n)^{77}Br	38 → 15	90, 91	good
					^{93}Nb(p, spall)^{77}Br	600	68	fair
^{77}Kr	1.2 h	β^+ (79.8), EC (20.2)	900 (4), 1550 (12), 1700 (36), 1875 (48)	130 (87.3), 147 (40.9), 511 (159.6)	^{79,81}Br(d, xn)^{77}Kr	86 → 20	17	good
					^{79,81}Br(p, xn)^{77}Kr	85 → 10	25, 31	good
					^{76}Se(^{3}He, 2n)^{77}Kr	34 → 12	35	good
					^{77}Se(^{3}He, 3n)^{77}Kr	36 → 18	35	good
↓ ^{77}Br	see above							
^{79}Kr	34.9 h	β^+ (6.9), EC (93.1)	613 (100)	261 (12.7), 397 (9.5), 511 (13.8), 606 (8.1)	^{79}Br(p, n)^{79}Kr	20 → 2	92	good
					^{79,81}Br(p, xn)^{79}Kr	85 → 10	25	fair
					^{79,81}Br(d, xn)^{79}Kr	86 → 10	17	good
^{81}Rb	4.6 h	β^+ (27), EC (73)	325 (10), 575 (16), 1050 (74)	446 (19), 511 (54)	^{82,83}Kr(p, xn)^{81}Rb	32 → 16	93	poor
					^{nat}Kr(p, xn)^{81}Rb	45 → 10	94	fair
↓ generator					^{82}Kr(d, 3n)^{81}Rb			
					^{85}Rb(p, p4n)^{81}Rb	70 → 45	95	good
					^{85}Rb(p, 5n)^{81}Sr; ^{81}Sr $\xrightarrow[25\ min]{\beta^+}$ ^{81}Rb	150 → 20	96	poor
^{81m}Kr	13.3 sec	IT (100)		191 (67)	^{79,81}Br(^{3}He, xn)^{81}Rb	40 → 13	97	fair
					^{79}Br(α, 2n)^{81}Rb	40 → 13	5, 97	good
					^{81}Br(α, 4n)^{81}Rb			
^{82}Sr	25.0 d	EC (100)			^{85}Rb(p, 4n)^{82}Sr	70 → 32	95	good
↓ generator					^{85}Rb(d, 5n)^{82}Sr			
					^{82}Kr(^{3}He, 3n)^{82}Sr			
					^{80}Kr(α, 2n)^{82}Sr			
^{82}Rb	1.3 min	β^+ (96), EC (4)	2570 (14), 3350 (86)***	511 (192), 776 (13.6)**	Zr, Nb, Mo(p, spall)^{82}Sr	600, 800	68	fair

Table 1. Continued

Radioisotope	Decay data: Half-life	Mode of decay (%)	End point energy of β groups keV (rel. %)	Principal γ-rays keV (% abundance)	Nuclear reaction cross section data: Principal nuclear reactions	Energy range (MeV)	Major references	status
^{87}Y	80.3 h	β^+ (0.2), EC (99.8)	451 (100)	485 (92)	$^{87}Sr(p, n)^{87}Y$	7 → 3	5	fair
					$^{88}Sr(p, 2n)^{87}Y$	33 → 15	5	good
					$^{86}Sr(d, n)^{87}Y$			
generator					$^{85,87}Rb(^3He, xn)^{87m}Y$	37 → 12	98	fair
↓					$^{87m}Y \xrightarrow[13\,h]{IT} {}^{87}Y$			
^{87m}Sr	2.8 h	EC (0.3), IT (99.7)		388 (82)	$^{85,87}Rb(\alpha xn)^{87m}Y$	60 → 12	98	fair
					$^{87m}Y \xrightarrow[13\,h]{IT} {}^{87}Y$			
^{94}Ru	51.8 min	EC (100)		367 (79.2), 891 (21)	$^{nat}Mo(^3He, xn)^{94}Ru$	36 → 12	51	good
					$^{92}Mo(\alpha, 2n)^{94}Ru$	40 → 20	95	good
^{95}Ru	1.6 h	β^+ (15), EC (85)	700 (7), 1010 (71), 1330 (22)***	336 (71), 627 (17.8), 1097 (21.3)	$^{nat}Mo(^3He, xn)^{95}Ru$	36 → 12	51	good
					$^{92}Mo(\alpha, n)^{95}Ru$	30 → 13	99	good
^{97}Ru	2.9 d	EC (100)		216 (86), 324 (10.3)	$^{nat}Mo(^3He, xn)^{97}Ru$	36 → 12	51	good
					$^{94}Mo(\alpha, n)^{97}Ru$	45 → 12	99	good
					$^{95}Mo(\alpha, 2n)^{97}Ru$	60 → 17	99	good
^{101m}Rh	4.4 d	EC (92.8), IT (7.2)		307 (87), 545 (4.1)	$^{101}Ru(p, n)^{101m}Rh$	6 → 3	5	poor
					$^{100}Ru(d, n)^{101m}Rh$			
					$^{103}Rh(p, 3n)^{101}Pd \xrightarrow[8.5\,h]{EC,\beta^+} {}^{101m}Rh$	37 → 25	100	poor
^{111}In	2.8 d	EC (100)		172 (87.6), 245 (94.2)	$^{111}Cd(p, n)^{111}In$	15 → 4	5	fair
					$^{110}Cd(d, n)^{111}In$			
					$^{109}Ag(^3He, n)^{111}In$	45 → 12	101	good
					$^{109}Ag(\alpha, 2n)^{111}In$	40 → 15	5	good
^{122}Xe	20.1 h	EC (100)		149 (3.2), 350 (8), 417 (2)**	$^{127}I(p, 6n)^{122}Xe$	85 → 55	102	fair
					$^{127}I(d, 7n)^{122}Xe$	90 → 55	29	good
generator					$^{133}Cs, {}^{139}La \}(p,x)^{121-127}Xe$	590 → 320	103, 104	good
↓								
^{122}I	3.6 min	β^+ (77), EC (23)*	2600 (10), 3100 (90)***	511 (154), 564 (18)**				
^{123}I	13.02 h	EC (100)		159 (83), 529 (1.05)	$^{123}Te(p, n)^{123}I$			
					$^{122}Te(d, n)^{123}I$			
					$^{124}Te(p, 2n)^{123}I$	30 → 10	11, 105, 106	good
					$^{121,123}Sb(^3He, xn)^{123}I$	26 → 12	107	good
					$^{121}Sb(\alpha, 2n)^{123}I$	28 → 9	107	good
^{123}Xe	2.08 h	β^+ (13) EC (87)	1550 (100)	149 (49), 178 (15), 330 (8.6)	$^{127}I(p, 5n)^{123}Xe$	160 → 20	102, 108–110	fair
					$^{127}I(d, 6n)^{123}Xe$	90 → 45	29	good
					$^{123}Te(^3He, 3n)^{123}Xe$	38 → 20	111	fair
					$^{124}Te(^3He, 4n)^{123}Xe$	52 → 28	111	fair
↓					$^{122}Te(\alpha, 3n)^{123}Xe$	43 → 34	112, 113	fair
^{123}I	see above				$^{127}I(\alpha, x)^{123}Xe$	110 → 85	9, 114	fair
					Cs, Ba, La (p, spall)^{123}Xe	590 → 200	68, 103	fair
					I, Cs, Ba, La } (p, spall)^{123}Xe	660	104	fair
^{125}Xe	16.8 h	β^+ (0.3), EC (99.7)	470 (100)	188 (55), 243 (28.7)	$^{127}I(p, 3n)^{125}Xe$	160 → 20	102, 108–110	fair
					$^{127}I(d, 4n)^{125}Xe$	90 → 25	29	good
					$^{nat}Te(^3He, xn)^{125}Xe$	40 → 10	115	good
					$^{nat}Te(\alpha, xn)^{125}Xe$	40 → 10	115	fair
					$^{127}I(\alpha, x)^{125}Xe$	100 → 75	114	fair
					Cs, Ba, La (p, spall)^{125}Xe	590 → 200	68, 103	fair
					I, Cs, Ba, La } (p, spall)^{125}Xe	660	104	fair
^{127}Cs	6.25 h	β^+ (3.5), EC (96.5)	650 (50), 1040 (50)	125 (12.1) 411 (62), 462 (5.2)	$^{127}I(\alpha, 4n)^{127}Cs$	150 → 40	8, 114	fair

Table 1. Continued

Radioisotope	Decay data				Nuclear reaction cross section data			
	Half-life	Mode of decay (%)	End point energy of β groups keV (rel. %)	Principal γ-rays keV (% abundance)	Principal nuclear reactions	Energy range (MeV)	Major references	Status
^{128}Ba ↓ generator ↓ ^{128}Cs	2.43 d 3.8 min	EC (100) β^+ (61), EC (39)	 1900 (8), 2445 (26), 2885 (66)	273 (14.5) 443 (25.8), 511 (122), 527 (2.3)	^{133}Cs(p, 6n)^{128}Ba ^{133}Cs(d, 7n)^{128}Ba	67 → 50	30	fair
^{129}Cs	32.06 h	EC (100)		372 (32), 411 (23.3), 549 (3.6)	^{127}I(α, 2n)^{129}Cs ^{133}Cs(p, 5n)^{129}Ba ^{129}Ba $\xrightarrow[2.2\,h]{\beta^+, EC}$ ^{129}Cs	150 → 20 67 → 35	8 30	fair good
^{167}Tm	9.25 d	EC (100)		208 (41), 531 (1.6)	^{167}Er(p, n)^{167}Tm ^{166}Er(d, n)^{167}Tm ^{165}Ho(α, 2n)^{167}Tm ^{nat}Er(^{3}He, pxn)^{167}Tm ^{nat}Er(α, pxn)^{167}Tm Lu, Hf, Ta, W (p, spall)^{167}Tm	 50 → 20 38 → 20 36 → 20 590	 5, 116 116 116 117	 good fair fair fair
^{201}Tl	73.5 h	EC (100)		166+167 (10.2), 135 (2.6)	^{202}Hg(p, 2n)^{201}Tl ^{nat}Hg(p, xn)^{201}Tl ^{203,205}Tl(p, xn)^{201}Pb ^{201}Pb $\xrightarrow[9.4\,h]{EC}$ ^{201}Tl ^{206}Pb(p, x)^{201}Tl Pb, Bi(p, spall)^{201}Tl	 50 → 14 60 → 15, 800	 118 15, 16, 119, 120 68	 poor good fair
^{203}Pb	52.1 h	EC (100)		279 (80.7), 401 (3.8)	^{203}Tl(p, n)^{203}Pb ^{205}Tl(p, 3n)^{203}Pb ^{204}Pb(d, 3n)^{203}Bi ^{203}Bi $\xrightarrow[11.8h]{EC, \beta^+}$ ^{203}Pb ^{203}Tl(^{3}He, 3n)^{203}Bi ^{203}Bi $\xrightarrow[11.8h]{EC, \beta^+}$ ^{203}Pb	16 → 7 60 → 20 27 → 20	16 15 121	fair good fair
^{211}At	7.2 h	α (41.94), EC (58.06)	α5866 (100)	687 (0.245)	^{209}Bi(α, 2n)^{211}At	45 → 20	5	good

* Branching ratio rather uncertain. ** γ-ray intensities rather uncertain. *** Intensities of β groups rather uncertain.

purposes are listed together with the energy range for each reaction and the major references [5–121]. Early references which are to be found in the compilation of KELLER *et al.* [5] are not given. It should be noted that citation was limited only to those papers which deal specifically with the problem of nuclear data. Several excellent publications dealing with the technical details of some production methods could not be considered since they were outside the scope of this review.

The status of the available nuclear reaction data is given in the last column of Table 1. The status termed as good, fair or poor is arbitrary and expresses more the opinion of the reviewer, rather than the absolute quality of the data. If no entry exists, it means that no measurement has been carried out (as far as we know). It should be emphasized here that in some cases the production methods have been excellently worked out though the reaction data have either not been measured or are only poorly characterized. The status of the cross section data should therefore under no circumstances be interpreted as the status of the art of production of a particular radioisotope.

From Table 1 it is evident that the data for the production of more commonly used radioisotopes (groups 1 to 4 in Fig. 8), especially via low-energy reactions, are fairly good. In other cases some gaps do exist.

5. Nuclear data needs

As discussed above the nuclear structure and decay data are well-known and the needs are commonly met by the existing data. Some special cases where uncertainties do exist are mentioned in Table 1. A few other isotopes needing revision or extension of the available decay data were identified recently [10].

Measurements on neutron induced reaction cross section data are generally motivated by energy research programmes. The existing data are sufficient for medical radioisotope production using nuclear reactors.

The cyclotrons and accelerators used for medical radioisotope production can be roughly divided into three groups:

(i) Low-energy machines ($E \leqslant 15$ MeV), including Baby-Cyclotrons, associated with hospitals. These are used mainly for the on-site production and application of short-lived β^+-emitting nuclides like ^{11}C, ^{13}N and ^{15}O.

(ii) Multipurpose multiparticle medium-energy machines ($E \leqslant 200$ MeV), including Compact Cyclotrons on the lower energy side of this group. A large variety of radioisotopes are produced using such machines.

(iii) High-energy machines ($E \geqslant 300$ MeV), accelerating mostly protons, are used basically for high-energy physics studies but some radioisotope production work is also carried out.

Table 1 shows that in the low-energy region the available cross section data are generally satisfactory. Except for the very light target nuclei the data needs could also be met by theoretical calculations. It would, however, be useful if for the commonly used β^+-emitters (^{11}C, ^{13}N, ^{15}O, ^{18}F) the existing experimental data could be evaluated. Some potentially useful ultra short-lived β^+-emitters like ^{17}F ($T_{1/2}$ = 64.5 sec), ^{19}Ne ($T_{1/2}$ = 17.4 sec), ^{21}Na ($T_{1/2}$ = 22.8 sec) etc., which could also be produced using low-energy reactions, are not listed in Table 1. The cross section data for those reactions are not known well. If the application of those radioisotopes is demonstrated, there will be need for more accurate data.

Since a greater part of the research and development work in the field of medical radioisotope production is performed in the medium-energy region, most of the nuclear data needs also arise in that energy region. Those needs may differ from one laboratory to another and depend upon such factors as the types of particles accelerated, the energy ranges considered, the particular route chosen for the production of an isotope, etc. The data needs are therefore difficult to define. Table 1, however, does give an idea on the reactions useful or potentially useful for the production of some important radioisotopes. It may be worthwhile to measure the unknown cross sections and to evaluate those where appreciable experimental information is available.

In the high-energy region ($E \geqslant 300$ MeV) the cross sections for the formation of the major products show relatively little dependence on the energy of the incident protons. One needs, therefore, mostly information on the production yields. The existing experimental data, systematic trends and calculational methods can reproduce yields of main products within a factor of 2. However, for products very near or very far from the target nucleus further experimental and theoretical studies are needed.

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Appendix II

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Production of Some Medically Important Short-Lived Neutron-Deficient Radioisotopes of Halogens

By S. M. QAIM and G. STÖCKLIN, Institut für Chemie 1 (Nuklearchemie), Kernforschungsanlage Jülich GmbH, D-5170 Jülich, FRG

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Short-lived radiohalogens /Medical isotope production /Radiation dose /Nuclear reactions /Excitation functions /Thick target yields / Targetry /Radiochemical separation /Radionuclidic impurity / Review

Summary

Halogens are particularly useful for designing structural analogues of biomolecules which find application in functional imaging using PECT (e.g. with ^{18}F, ^{75}Br) or SPECT (with ^{123}I). This paper reviews some of the recent information published on the production of ^{18}F, ^{34m}Cl, ^{77}Br, ^{75}Br, ^{123}I and ^{211}At. The nuclear reactions studied, the optimum energy ranges suggested, the thick target yields obtained (or expected) and the radionuclidic impurities found in each process are briefly summarized. A short outline of the state of the art of targetry for the production of each radioisotope is given. The radiochemical separation methods are discussed. Wherever possible a critical comparison of the various production routes is given.

Introduction

Functional imaging has greatly stimulated nuclear medicine and radiopharmaceutical research. The search for new agents is not limited to natural body constituents and their precursors; it also includes their chemical analogues.

Metabolites and other organic body constituents consist of carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulphur atoms in various combinations, and the ideal tracer is a radioisotope of these constituent atoms. Unfortunately, the number of these radioisotopes with useful nuclear properties for *in vivo* application is very limited. Only the organic positron-emitters ^{11}C ($t_{1/2}$ = 20 min), ^{13}N ($t_{1/2}$ = 10 min), ^{15}O ($t_{1/2}$ = 2.1 min), and ^{30}P ($t_{1/2}$ = 2.5 min) can principally fulfill the requirement of leaving the cell physiology of a particular carbon, nitrogen, oxygen, or phosphorus-containing biomolecule *a priori* unchanged. Among these organic positron-emitters only ^{11}C is useful for labelling more complicated organic molecules applicable to metabolic studies, provided the desired labelling process can be completed within two to three half-lives. Furthermore, application requires an in-house cyclotron and is restricted to fast metabolic processes. In addition, it is extremely difficult to achieve specific activities in the order of several 100 to 1000 Ci mmol^{-1} [1 – 3] which are often mandatory for receptor studies or the application of potent drugs.

It is therefore not surprising that the analogue approach has been extensively explored during the past years. In functional imaging with positron-emission computed tomography (PECT), the most successful example is the use of ^{18}F ($t_{1/2}$ = 110 min) as 2-fluoro-2-deoxyglucose (FDG) instead of 2-deoxyglucose for quantitative assessment of regional glucose utilization [4, 5]. In the case of photon emitters which can be used in conjunction with single-photon emission computed tomography (SPECT), advances have been limited by the slow progress in the development of useful radiopharmaceuticals. The most prominent example for the analogue approach is the introduction of ^{123}I ($t_{1/2}$ = 13.2 h) as an "organic" labelling atom due to its ideal nuclear properties (see below).

Halogens are particularly useful, since they form covalent bonds with carbon atoms and can thus be considered as organic radioisotopes [6]. Structural analogues can easily be designed. The medically important halogen radioisotopes and their major decay characteristics are listed in Table 1 [cf. 7]. Fluorine-18 is an ideal positron emitter for PECT. Its half-life is convenient and even allows shipment within a range of at least 100 km. Its small β^+ energy is advantageous with respect to resolution in PECT, the linear range of β^+_{max} being 2.3 mm in water. Chlorine-34m is the only radioisotope of chlorine of potential medical interest, but its low positron emission rate together with its high positron energy make it less useful for PECT. The bromine radioisotopes of interest are those of mass number 74 to 77. The positron emitter Bromine-74m is not easy to prepare in sufficient quantities, and in addition it has a very high positron energy. Bromine-75, on the other hand, is the most useful radioisotope of bromine, having a convenient half-life and a reasonable positron energy with a linear range of β^+_{max} of 8.0 mm in water. A simplified decay scheme of this radioisotope is given in Fig. 1. One disadvantage is the 286 keV γ-line from the 1.3 nsec excited state of selenium-75 populated in the decay of ^{75}Br. With present-day PECT machines this gives rise to random coincidences and hence to poor image contrast. There are, however, possibilities to avoid or to correct this. Another disadvantage is that the daughter selenium-75 ($t_{1/2}$ = 120 d) adds to the radiation dose to the patient, although the contribution from the longer-lived selenium-75 is generally small. If complete decay of homogeneously-distributed bromine-75 occurs, the whole body dose is 78 mrad/mCi [8], and only one third of this dose is due to selenium-75. This whole body dose is a factor of 3 smaller than that from bromine-77 and a factor of 14 smaller than that from bromine-76. Bromine-76 has a high positron energy and a low positron emission rate. Together with its relatively long half-life this leads to considerably higher dose to the patient. Nevertheless, this radioisotope seems to be

Table 1. *Decay characteristics of some medically important radioisotopes of halogens*

Radioisotope	$T_{1/2}$	Mode of decay (%)	E_{β^+} (max) keV	Main γ-rays keV (%)	Imaging device
^{18}F	1.83 h	β^+ (97) EC (3)	635		Positron tomograph
^{34m}Cl	32 min	β^+ (53) IT (47)	4500	146 (41) 2127 (42)	Conventional γ-camera; positron tomograph
^{75}Br	1.63 h	β^+ (75.5) EC (24.5)	1740	286 (91.6) 141 (7)	Positron tomograph
^{77}Br	56 h	β^+ (0.7) EC (99.3)	336	239 (22.8) 521 (22.1)	High-energy collimator camera
^{123}I	13.2 h	EC (100)		159 (83)	Conventional γ-camera; SPECT
^{211}At	7.2 h	EC (58)* α (42)	5866 (α_0)	687 (0.24)	

* 100% including the decay of the 0.52 sec ^{211}Po daughter.

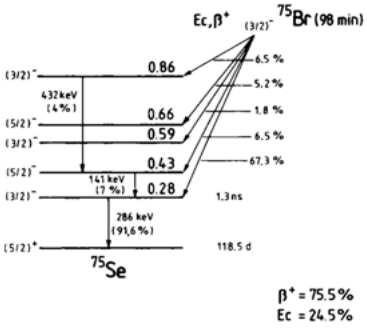

Fig. 1. Simplified decay scheme of ^{75}Br.

suitable for PECT studies with animals. Bromine-77 is a photon emitter with a convenient half-life for longer lasting studies. Its 521 keV γ-line, however, is not suitable for conventional γ-cameras and requires high-energy collimation. Iodine-123 is the most suitable isotope for SPECT, and considerable efforts have been made all over the world to produce it in sufficient quantities and with high radionuclidic purity. As a result this radionuclide is now commercially available, even though the price is high and good radiopharmaceuticals are sparse. The artificial radioelement astatine has α-emitting radioisotopes which are of potential interest for radiation therapy and biology. Astatine-211 in particular has found wide interest as an internal α-source because of its high α-emission rate (100% including the ultra short-lived ^{211}Po-daughter) and its suitable half-life. The long-lived ^{207}Bi-daughter does not contribute to the dose.

Production methods

For production of the above mentioned radiohalogens a variety of nuclear reactions, target systems and radiochemical separation methods have been used. The status of nuclear data has been recently reviewed [10]. Here we discuss other aspects related to the production of each individual radioisotope.

Fluorine-18

Methods used for the production of this radioisotope have been reviewed [cf. 11, 12]. It should be emphasized that in general the production of this radioisotope is less problematic than obtaining it in a chemical form useful for subsequent chemistry. The radioisotope can be produced using either nuclear reactors or cyclotrons. Production in nuclear reactors is done via the $^{16}O(t, n)^{18}F$ reaction. The tritons with E_{max} = 2.7 MeV are generated by the $^{6}Li(n, \alpha)^{3}H$ reaction. The target material is generally Li_2CO_3 with a ^{6}Li-enrichment of at least 90%. ^{18}F is recovered as $^{18}F^-$ and many methods such as extraction, distillation, ion-exchange chromatography, coprecipitation, etc., have been used for the separation of ^{18}F from the target [cf. 13]. Tritium is a major radioactive impurity produced during the reaction, but in a good separation its content can be reduced to $< 0.5\%$. ^{18}F can also be produced via $^{19}F(n, 2n)^{18}F$, $^{19}F(p, pn)^{18}F$ [cf. 14] and $^{19}F(\gamma, n)^{18}F$ [15, 16] reactions. In these methods carrier is necessarily introduced, but reasonable yields may be obtained for tracer experiments.

Large scale production of high-specific activity ^{18}F is carried out using cyclotrons. In general, oxygen or neon is used as target material. A summary of recent studies using various processes is given in Table 2 and the yields expected from the five major processes, *viz.* $^{16}O(^{3}He, p)^{18}F$, $^{16}O(\alpha, d)^{18}F$, $^{18}O(p, n)^{18}F$, $^{20}Ne(d, \alpha)^{18}F$ and $^{20}Ne(^{3}He, \alpha p)^{18}F$, are given in Fig. 2. The ^{3}He- and α-particle induced reactions on ^{16}O lead mostly to the direct formation of ^{18}F; the cross sections for the formation of ^{18}F via the decay of 1.7 sec ^{18}Ne are unknown but the total contribution is known to be minor [cf. 17, 19]. In production runs, both ^{3}He- and α-particle induced

Table 2. *Summary of methods for the production of "no-carrier added" ^{18}F*

Nuclear reaction	Energy range (MeV)	Theoretical [or experimental] thick target yield (mCi/μAh)	Impurities at EOB (%)	Type of work done	References
$^{16}O(^3He, p)^{18}F$ + $^{16}O(^3He, n)^{18}Ne \xrightarrow{\beta^+} {}^{18}F$	42 → 3	12.5	$^7Be(?)$, $^{11}C(?)$	Cross sections	17, 18
	41 → 14	13, [10]	^7Be (0.025), ^{11}C, ^{13}N ($< 10^{-3}$)	Cross sections; water target	19
	27 → 0	[6.7]	$^{11}C(?)$, $^{13}N(?)$	Closed-loop water target for internal beam up to 15 μA	20
$^{16}O(\alpha, d)^{18}F$ + $^{16}O(\alpha, 2n)^{18}Ne \xrightarrow{\beta^+} {}^{18}F$	40 → 22	10.5	$^7Be(?)$	Cross sections	17
	52 → 4	[7]		Closed-loop water target for medium intensity (< 10 μA) internal beam	21
	55 → 0	[7]	^{32}P (0.01)	Medium current (< 10 μA) SiO_2 target; $^{18}F^-$ extraction with solvents	22
$^{18}O(p, n)^{18}F$	15 → 2	72		Cross sections; $^{18}O_2$ gas (91.7% enriched) target	25
	20 → 3	90		Yield considerations; high-current $H_2{}^{18}O$-target design	23, 24
	10 → 0	[50]		Low current (2 μA) $^{18}O_2$ gas target; stainless steel vessel with glass liner; cryogenic separation of $^{18}O_2$; rinsing of $^{18}F^-$ with solvents	26–28
$^{20}Ne(d, \alpha)^{18}F$	15 → 0	[28]		Medium current (up to 20 μA) neon gas target, Al vessel with glass liner	30
	18 → 2	34		Cross sections	17, 18, 29
	11 → 0	$\left[\begin{smallmatrix}8.8\\ {}^{18}F\text{-}F_2\end{smallmatrix}\right]$		High current (up to 40 μA) target containing pressurized Ne (+0.1% F_2) with internally F_2 passivated Ni vessel; removal of anhydrous ^{18}F-F_2 by purging, also dynamic removal.	14, 31, 32
				Ne/H_2 target to produce $H^{18}F$	14, 33, 34
$^{20}Ne(d, x)^{18}Ne \xrightarrow{\beta^+} {}^{18}F$	65 → 60	5		Cross sections up to 80 MeV	29
$^{20}Ne(^3He, \alpha p)^{18}F$	35 → 5	17		Cross sections	17
$^{20}Ne(^3He, \alpha n)^{18}Ne \xrightarrow{\beta^+} {}^{18}F$	33 → 17	0.1		Cross sections	29
$^{20}Ne(^3He, \alpha p)^{18}F$ + $^{20}Ne(^3He, \alpha n)^{18}Ne \xrightarrow{\beta^+} {}^{18}F$	56 → 10	25		Yield measurement; targetry similar to the (d, α) reaction	14
	27.5 → 0	$\left[\begin{smallmatrix}5.4\\ H^{18}F\end{smallmatrix}\right]$		High current (up to 30 μA) gas target (2 bar Ne + 2% H_2), 1.8 m^3/h flow, for $H^{18}F$ production	35, 36

reactions have been used. However, due to the higher energy needed in the latter case, use of the ^{3}He-particles has been more common. Though irradiation of a solid target (e.g. SiO_2) followed by ^{18}F extraction by various solvents has been employed [cf. 22], in general use of sterile and pyrogen-free water as target material has proven to be more convenient, both for internal and extracted beams. The circulating water is passed through a heat exchanger, thereby also serving as the cooling medium. The radiolysis of water and consequent formation of gaseous products, however, limits the maximum beam intensity to be used in irradiations. The gaseous products, being inactive, are generally allowed to escape into the atmosphere. After the end of the bombardment the water passes through an anion-exchange column, where ^{18}F is trapped. Thereafter it is eluted from the column with a small amount of isotonic saline solution. The final product obtained is $^{18}F^-$ and is very pure. The level of detected impurities (^{11}C, ^{13}N, ^7Be) is negligibly small [19].

The reaction $^{18}O(p, n)^{18}F$ leads to very high yields of ^{18}F. Design studies [23, 24] on a 98% enriched $H_2{}^{18}O$ target and cross section measurements using low current irradiations of gaseous ^{18}O enriched targets [25] showed that this reaction is of great potential. Two target systems have been recently developed [26–28] for irradiations at low to medium currents. In one system a small volume stainless steel chamber containing a 10 ml glass test tube with a silvered interior is used. The $^{18}O_2$ target

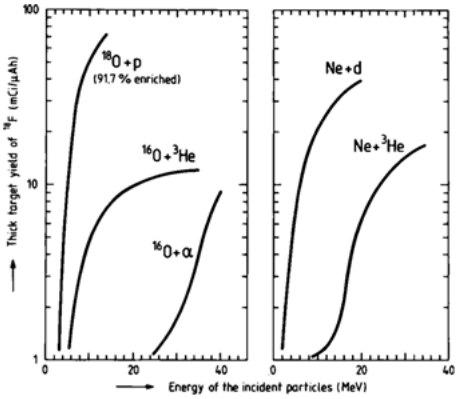

Fig. 2. Theoretical thick target yields of ^{18}F expected from various reactions on oxygen and neon isotopes. Data for the $^{16}O+^{3}He$, $^{16}O+\alpha$, Ne + d and Ne + ^{3}He were deduced from NOZAKI *et al.* [17] and for the ^{18}O + p reaction from RUTH and WOLF [25].

gas is admitted, irradiated, then retrieved into a reservoir by cryogenic pumping. The ^{18}F produced is deposited on the inner surface of the target liner. This liner is removed and serves as the reaction flask for various syntheses involving $^{18}F^-$. Maximum isolated yields of $^{18}F^-$ are obtained by using H_2O (95 °C, 10 min, 80%) and HF (50 °C, 2 min, 99%) as rinsing agents. In the second system a production scheme for ^{18}F-labelled F_2 has been developed. A passivated nickel target (see below) is first charged with pure $^{18}O_2$ (5.5 cm, 20 bar) and irradiated with 10 MeV protons. The ^{18}F activity is adsorbed on the target walls, permitting quantitative cryogenic retrieval of the enriched target gas. The target is then filled with the purge gas (Ne + 1% F_2) and again irradiated in order to induce isotopic exchange reactions between the adsorbed ^{18}F and the molecular F_2. The batch yield of $^{18}F-F_2$ obtained so far, however, is somewhat lower than that in the case of the $^{20}Ne(d, \alpha)^{18}F$ reaction (see below).

Often, water targets are not particularly useful for further synthetic application of Fluorine-18, since the solvated fluoride is very unreactive and the water has to be removed completely. Anhydrous precursor preparation via Ne gas target containing additives (see FERRIERI and WOLF, this issue) is more useful. ^{18}F is obtained as either ^{18}F-labelled F_2 or as $H^{18}F$ when F_2 or H_2, respectively, is added. Both d- and ^{3}He-induced nuclear reactions have been used, and cross section data have been measured accurately for the formation of ^{18}F both directly [17, 18, 29] and via the ^{18}Ne (1.7 sec) precursor [29].

The $^{20}Ne(d, \alpha)^{18}F$ reaction has been in use for quite some time [cf. e.g. 30] and relatively large yields have been reported; the chemical form of ^{18}F, however, was not always well defined. Extensive studies on the characterization of conditions of ^{18}F-labelled F_2 production have been carried out at BNL [14, 31, 32]. The target vessel is made of nickel (2.5 cm $\phi \times$ 10 cm) and the interior of the vessel is passivated by F_2. The vessel is filled with the highest purity Ne (plus F_2 in the range of 0.1 – 7.5%) and after irradiation the $^{18}F-F_2$ is purged out. Both static and dynamic removal has been investigated, though the static removal appears to be preferred. The removal yield is a function of target pressure and carrier concentration, increasing with increasing target pressure and decreasing with decreasing carrier concentration. At a target pressure of 24 bar and a carrier concentration of 0.1% F_2 the removal yield is nearly 75%. The yield of $^{18}F-F_2$ was also found to be strongly dependent on the levels of N_2, CO_2 and CF_4 impurities present in the target gas mixture, the upper acceptable limit for each of the three impurities being < 0.01%. The $^{18}F-F_2$ production method developed by the BNL group is now used in several laboratories, especially for the subsequent synthesis of [^{18}F]-FDG.

If the gas mixture used as target material is Ne/H_2 the product obtained is $H^{18}F$ [cf. 14, 33]. However, reproducible and nearly quantitative recoveries of $H^{18}F$ have not been reported. FERRIERI *et al.* [34] recently described a CF_4-H_2-Ne gas target for obtaining reproducibly high yields of anhydrous $H^{18}F$ via the $^{20}Ne(d, \alpha)^{18}F$ reaction. Under the influence of radiation, HF is generated radiolytically from CF_4 and reacts with the ^{18}F formed via the nuclear reaction. Optimum yields are obtained when the $H_2 : CF_4$ ratio is > 3.

In contrast to the $^{20}Ne(d, \alpha)^{18}F$ reaction, the $^{20}Ne(^{3}He, \alpha p)^{18}F$ reaction has not been widely used, possibly due to two reasons: firstly, the yields are about 30% lower and secondly, ~ 30 MeV ^{3}He-beams are not available in many laboratories. The Orsay group reported a dynamic system using a target consisting of Ne + 2% H_2 gas mixture in a nonpassivated nickel vessel [35, 36]. Irradiation was done with 27.5 MeV ^{3}He-beams at 30 μA. The $H^{18}F$ produced was removed instantaneously by the gas flow. It was postulated that most of the recovered ^{18}F was formed via the decay of ^{18}Ne. Recent nuclear data measurements [29] have shown that this assumption is not correct; the $H^{18}F$ obtained, nonetheless, should be anhydrous. For large scale production of $H^{18}F$ via this method further optimization work appears necessary.

As a conclusion it may be mentioned that for the production of ^{18}F the reactions $^{16}O(^{3}He, p)^{18}F$ and $^{20}Ne(d, \alpha)^{18}F$ have been most commonly used, the former for producing $^{18}F^-$ and the latter for obtaining anhydrous ^{18}F. Whereas production of both $^{18}F-F_2$ and $H^{18}F$ has been achieved, detailed optimization of only the $^{18}F-F_2$ production has been carried out. The $^{18}O(p, n)^{18}F$ reaction has great potential for production at low energy machines.

Chlorine-34m

A summary of the methods suggested for the production of ^{34m}Cl in a "no-carrier added" form is given in Table 3. Cross sections and yields of ^{34m}Cl formed in the inter-

Table 3. *Summary of methods suggested for the production of "no-carrier added"* ^{34m}Cl

Nuclear reaction	Energy range (MeV)	Theoretical [or experimental] thick target yield (mCi/μAh)	Impurities (%)	Type of work done	References
^{31}P(α, n)^{34m}Cl	45 → 10	12		Yield measurement	37
^{nat}S(p, xn)^{34m}Cl	22 → 8	2.4		Yield measurement	37
^{32}S(^{3}He, p)^{34m}Cl	25 → 5	2.8		Cross sections	38
	30 → 5	3.8		Yield measurement	37
^{32}S(α, pn)^{34m}Cl	45 → 20	38		Yield measurement	37
^{35}Cl(p, pn)^{34m}Cl	24 → 12	34		Cross sections; low-current K_2ReCl_6 target; Szilard-Chalmers separation	39
		[1.5 after Szilard-Chalmers separation]	none		

actions of ^{31}P and ^{32}S with α-particles [37], ^{32}S with ^{3}He-particles [37, 38] and ^{nat}S and ^{35}Cl with protons have been reported [37, 39]. However, most of those studies were performed in connection with the activation analysis of P, S and Cl using charged particles. For medical applications ^{34m}Cl was produced via the ^{35}Cl(p, pn)^{34m}Cl reaction [39]. A K_2ReCl_6 target was irradiated with 24 MeV protons at beam currents of a few μA, and practically carrier-free ^{34m}Cl was separated by the Szilard-Chalmers process [40]. The chloride yield is around 15% and is strongly dependent on the temperature. Due to the limited use of ^{34m}Cl, not much effort has been devoted towards development of high-current targets for the production of this radioisotope.

Bromine-77

Methods for the production of this radioisotope have been reviewed [cf. 6]. Here we discuss the recent information in detail. A summary of the suggested methods is given in Table 4. A variety of nuclear reactions [41–62] induced by p, d, ^{3}He and α-particles on target elements arsenic, selenium and bromine, as well as the spallation of molybdenum with 800 MeV protons, have been used.

For arsenic as target element the (α, 2n) reaction is most commonly used. The initial cross section measurements [41, 42] have recently been extended up to 120 MeV [43]; the optimum energy range being, however, $E_\alpha = 30 \rightarrow 14$ MeV. Starting from selenium, proton and ^{3}He-particle induced reactions have been investigated [42, 44, 45, 53–56]. Production of ^{77}Br from bromine as target element generally involves the use of the ^{77}Kr → ^{77}Br precursor system. The suitability of this method was first investigated at Jülich [46]. Subsequently the (p, xn)-reactions were used by several groups [47–49, 57–60], although the cross section data for these reactions are still somewhat discrepant. The spallation process is limited to high-energy machines.

In contrast to the relatively large number of publications dealing with cross sections and yield measurements, the available information on high-current targets needed for large scale production of ^{77}Br is rather scanty. First systematic efforts were carried out at Hammersmith [50, 51] and As, As_2O_3 and As_2O_5 were used as target materials. Separation of radiobromine was carried out via wet chemical distillation and the batch yields of ^{77}Br achieved were about 12 mCi (at EOB). Some mixed arsenic oxides were tried but were found to be suitable only for low to medium current irradiations [42, 45]. The intermetallic compound Pb^{78}Se, investigated at BNL, was found to withstand beam currents up to 15 μA. The separation of radiobromine and recovery of the enriched ^{78}Se, however, place heavy demand on radiochemical work. As far as the ^{77}Kr → ^{77}Br precursor method is concerned, an on-line system for removing ^{77}Kr from a NaBr target was first reported by the Jülich group [46]. However, the system can withstand only medium power densities. Use of the same target material in a batch process [cf. 56] may be able to withstand higher power densities. The short half-life of the precursor, however, limits the batch yield of ^{77}Br to a few mCi.

Recent advances in targetry and chemical processing relevant to large scale production of ^{77}Br have been reported from Jülich [52] and Los Alamos [62], making use of the ^{75}As(α, 2n)^{77}Br and Mo (p, spall)^{77}Br processes, respectively. A high current Cu_3As-alloy used in the former process is capable of withstanding power densities of up to 2100 W cm^{-2}. Irradiations are carried out for 6 hr with 28 MeV α-particles at 100 μA (internal beam). Radiobromine is separated without adding any carrier via distillation at 950 °C in an automated apparatus (more details are given below in connection with the production of ^{75}Br). The batch yield is about 50 mCi (at EOB) and the separated radiobromine in aqueous solution exists > 95% as ^{77}Br$^-$. In the spallation process a 1-cm thick Mo-sheet is irradiated for 3 to 4 days with 800 MeV protons at ~ 500 μA in a parasitic position. The spallation products are allowed to cool for some time and then radiobromine is separated by a wet chemical process. The batch yield is about 300 mCi and the product exists as ^{77}Br$^-$. It should be emphasized here that the relatively long half-life of ^{77}Br compared to other radioisotopes of bromine and the parasitic use of the beam render the spallation process for the production of ^{77}Br very attractive.

Table 4. *Summary of methods suggested for the production of "no-carrier added" ^{77}Br*

Nuclear reaction	Energy range (MeV)	Theoretical [or experimental] thick target yield (mCi/μAh)	Impurities at EOB (%)	Type of work done	References
^{75}As(α, 2n)^{77}Br	28 →21	[0.16 from As_2O_5]	^{76}Br(<1)	Small scale production; As_2O_5 as target material; wet chemical processing	50
	28 →14			Cross sections up to 120 MeV	41, 43
	28 →14	0.50 [0.29 from As_2O_3]		High current (up to 70 μA) As and As_2O_3 targets; wet chemical processing	51
	30 →14	0.64	^{76}Br(5.5)	Cross sections; medium current mixed arsenic oxides as targets; wet chemical processing	42, 56
	28 →14	[0.09 from Cu_3As]	None	Cu_3As alloy as high current (up to 120 μA) target; dry distillation of ^{77}Br; large scale production	52
^{77}Se(p, n)^{77}Br	13.5→ 0	[0.5]		Yield measurement	53
	12 → 9	[0.5]	^{76}Br(2.5), ^{82}Br(0.25)	94.4% enriched ^{77}Se metal target for medium currents; wet chemical processing	54
	12 → 9	[0.43]	^{76}Br(7.7), ^{82}Br(1.4)	92.4% enriched ^{77}Se for yield measurement; sod. selenate target for medium currents	45
^{78}Se(p, 2n)^{77}Br	33 →26	[1.8 from $Pb^{78}Se$]		$Pb^{78}Se$ (98.6% enriched) target for currents up to 15 μA; wet chemical processing and ^{78}Se recovery	55
	25 →20	[4.3]	^{76}Br(0.5), ^{82}Br(0.01)	97.9% enriched ^{78}Se for yield measurements; sod. selenate target for medium currents	45
^{nat}Se(p, xn)^{77}Br	30 →15	3.5	^{76}Br(148), ^{82}Br(16)	Cross sections; mixed oxides as target for medium currents	42, 56
^{nat}Se(^{3}He, pxn)^{77}Br	38 → 0	0.01	^{76}Br(41)	Na_2Se target for yield measurement	59
^{76}Se(^{3}He, pn)^{77}Br	22 →15	0.2	^{76}Br(5)	Cross sections using 96.9% enriched ^{76}Se	44
^{77}Se(^{3}He, p2n)^{77}Br	30 →15	0.45	^{76}Br(1.1)	Cross sections using 94.4% enriched ^{77}Se	44
^{79,81}Br(p, xn)^{77}Kr ^{77}Kr $\xrightarrow[1.2\,h]{\beta^+,EC}$ ^{77}Br	45 →15			Yields; cross sections up to 90 MeV	57, 49
	40 →15	1.3	^{76}Br(1.7)	Cross sections	42, 56
	32 →23	[0.46 from KBr]	None	Medium current KBr target; dynamic removal of radiokrypton	58
	45 →30	2.0	^{76}Br(<0.5)	Cross sections	47
	65 →25	[1.6 from KBr]		Cross sections; KBr target for low currents; batch removal of radiokrypton	48, 59
	45 →32	1.3		Cross sections; batch separation	60
^{79,81}Br(d, xn)^{77}Kr ^{77}Kr $\xrightarrow[1.2\,h]{\beta^+,EC}$ ^{77}Br	50 →25	0.64	^{76}Br(4.0)	Cross sections; NaBr target for medium currents; on-line removal of radiokrypton	46
^{79,81}Br(α, xn)^{77}Rb ^{77}Rb $\xrightarrow[4\,min]{\beta^+}$ ^{77}Kr $\xrightarrow[1.2\,h]{\beta^+,EC}$ ^{77}Br	102 →70	[0.04]		Yield measurement	61
Mo(p, spall)^{77}Br	800	[0.012]	^{76}Br(<2), ^{82}Br(0.4)	1 cm thick high current Mo target; wet chemical processing; large scale production	62

Bromine-75

The use of this radioisotope in nuclear medicine was first suggested by the Jülich group [8]. Subsequently several other laboratories also reported its small scale production [63, 64]. A summary of the suggested methods of production is given in Table 5.

There are four possible routes for the production of ^{75}Br, namely the ^{3}He- or α-particle induced reactions on arsenic, the p- or d-induced reactions on enriched ^{76}Se, the ^{75}Kr $\xrightarrow[4.2\ \text{min}]{\beta^+,\ \text{EC}}$ ^{75}Br precursor system, and the ^{78}Kr(p, α)^{75}Br reaction on enriched ^{78}Kr.

The ^{75}Kr → ^{75}Br precursor system [65] leads to very low yields of ^{75}Br and is therefore not of practical value. The ^{78}Kr(p, α)^{75}Br reaction may be feasible [66] for medium scale production at low energy machines if technology for handling highly expensive ^{78}Kr is developed; large batch yields, however, are not to be expected. The (p, 2n) and (d, 3n) reactions on ^{76}Se are expected to give very high thick-target yields. As far as yield and ^{76}Br-impurity are concerned, the proton induced reaction is optimal. The separation of radiobromine by wet chemical methods and the recovery of enriched ^{76}Se may present some difficulties. Large scale production of ^{75}Br via this route has therefore so far not been reported. Presently, the choice lies on the use of arsenic as target material. Although the ^{75}As(α, 4n)^{75}Br reaction gives reasonable yield, the rather high-energy α-particles needed and the level of ^{76}Br impurity are the major drawbacks in the use of this reaction. The method of choice is presently the ^{75}As(^{3}He, 3n)^{75}Br reaction. Targetly problems related to this process have been extensively studied at Jülich [52]. The high current Cu_3As-alloy target, described above for the production of ^{77}Br, is also used for the production of ^{75}Br. Irradiations are done with 36 MeV ^{3}He-particles using an automatic internal target system shown schematically in Fig. 3 [67].

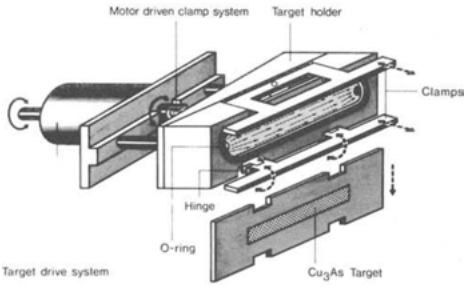

Fig. 3. Sketch of remotely controlled target system for irradiations in the internal beam [67].

The beam falls at an angle of 3.2° and cooling is done only from the back of the target holder. Incident beam currents of about 100 μA are used. Radiobromine is separated from the irradiated target material in a "no-

Table 5. *Summary of methods suggested for the production of "no-carrier added" ^{75}Br*

Nuclear reaction	Energy range (MeV)	Theoretical [or experimental] thick target yield (mCi/μAh)	Impurities at EOB (%)	Type of work done	References
^{75}As(^{3}He, 3n)^{75}Br	36 → 25	8	^{76}Br(2.1), ^{77}Br(0.07)	Cross sections; radiation dose calculations; medium scale production	8
				Small scale production	63
	34 → 24	6	^{76}Br(4.0), ^{77}Br(?)	Cross sections	64
				Cross sections up to 70 MeV	43
	36 → 25	[1.5 from Cu_3As]	^{76}Br(3.4), ^{77}Br(0.05)	Cu_3As alloy as high-current (150 μA) target material; dry distillation of radiobromine; automation	52
^{75}As(α, 4n)^{75}Br	65 → 54	7.5	^{76}Br(6.0), ^{77}Br(?)	Cross sections up to 115 MeV	64, 43
^{76}Se(p, 2n)^{75}Br	28 → 22	118	^{76}Br(1.4), ^{77}Br(?)	Cross sections on 92.4% enriched ^{76}Se	64
^{76}Se(d, 3n)^{75}Br	35 → 29	82	^{76}Br(4.4), ^{77}Br(?)	Cross sections on 92.4% enriched ^{76}Se	64
^{76}Se(^{3}He, p3n)^{75}Br	36 → 28	0.5	^{76}Br(284), ^{77}Br(24)	Cross sections on 96.9% enriched ^{76}Se	44
^{79,81}Br(d, xn)^{75}Kr ^{75}Kr $\xrightarrow[4.2\,\text{min}]{\beta^+,\ \text{EC}}$ ^{75}Br	90 → 68	0.21 *	^{76}Br(0.4), ^{77}Br(5.7)	Cross sections	65
^{78}Kr(p, α)^{75}Br	15 → 12	2 **	^{76,77}Br(0.1)	Feasibility study	66

* Due to the short-life of the ^{75}Kr precursor only batch yields are meaningful. This value gives the yield of ^{75}Br under optimum conditions: E_d = 90 → 68 MeV, irradiation time 8.5 min, rapid separation of radiokrypton, growing in time of ^{75}Br 8.0 min.

** With 100% enriched ^{78}Kr, 31 cm target length, 2 bar (extrapolated experimental yield).

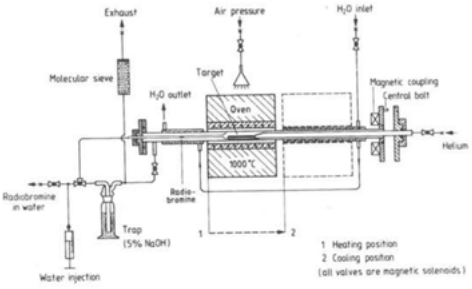

Fig. 4. Schematic diagram of remotely controlled automated apparatus for dry distillation of radiobromine from irradiated Cu,As-alloy [52].

carrier added" form via dry distillation at ~ 950 °C. The distillation apparatus is shown in Fig. 4. Radiobromine separated from the target is carried over by a helium stream and condenses in the middle of the stainless steel tube. Arsenic and selenium distill only negligibly and condense at the end of the stainless steel tube near the oven. Radiobromine is dissolved in 0.5 ml of water. The yield of radiobromine separated by this thermochromatographic method is > 90%. Radiochromatographic analysis showed that radiobromine appears only as $^{75}Br^-$. The batch yields of ^{75}Br are ~ 200 mCi. In order to cope with the high level of activity the distillation apparatus has been completely automated and is controlled by a microcomputer [68].

Iodine-123

For the production of ^{123}I a large number of nuclear reactions have been investigated, and the available information has been critically evaluated in several publications [cf. 6, 69–72]. In the present review we shall therefore consider only some selective features of the older works and discuss the relatively recent studies in more detail.

The various nuclear processes leading to the formation of ^{123}I can be grouped under two general headings.

i) Direct methods
ii) Indirect methods, i.e. those which make use of the $^{123}Xe \xrightarrow[2.08\ h]{EC,\beta^+} {}^{123}I$ precursor system.

In the case of direct methods low energy (but high-intensity) cyclotrons are generally used; in the indirect methods, on the other hand, medium and high energy machines are necessary.

A summary of the direct methods of production [73–84] is given in Table 6. These consist of α- and ^{3}He-particle induced nuclear reactions on antimony, as well as proton and deuteron induced reactions on isotopically enriched tellurium targets. The major impurity associated with these processes is the 4.15 d ^{124}I. The α- and ^{3}He-particle induced reactions on antimony give relatively low yields of ^{123}I and high levels of ^{124}I-impurity. Furthermore, construction of high-current targets using antimony is not easy. These reactions are therefore seldom used for production purposes.

Of the three reactions induced on tellurium isotopes, namely, ^{124}Te (p, 2n)^{123}I, ^{123}Te (p, n)^{123}I and ^{122}Te (d, n)^{123}I, the (p, 2n) reaction has been most extensively investigated. Precise cross section data measurements using various ^{124}Te-enrichments have been performed [cf. 76] and considerable advances in targetry and chemical separation of radioiodine have been reported [cf. 77, 78, 80, 81]. Two approaches have been utilized. Firstly, irradiation of 2 π or 4 π water-cooled ^{124}Te-metal target at medium currents (< 10 μA), followed by wet chemical separation of radioiodine and recovery of the enriched ^{124}Te-target material has been reported [cf. 77]. Secondly, irradiation of 4 π water-cooled $^{124}TeO_2$ target at medium to high currents (up to 45 μA), followed by dry distillation of radioiodine at 755 °C has been accomplished [cf. 78, 80, 81]. The second process is more convenient and is commonly used. A sketch of the target system used for these irradiations at Jülich [81] is given in Fig. 5. The $^{124}TeO_2$ is molten on a Pt backing and adheres to it well. The front side of the target is in direct contact with a thin layer of cooling water. The back side is also cooled by water. The loss of $^{124}TeO_2$ during a 1 hr irradiation at 30 μA is ⩽ 1%. A sketch of the apparatus used for dry distillation of radioiodine is shown in Fig. 6. The procedure was first suggested by the Eindhoven group [78] and has been further optimized at Jülich [81] using induction heating. The loss of $^{124}TeO_2$ during distillation is < 1% and the target is regenerated for immediate reuse. The radioiodine collected in water exists > 93% as iodide [cf. 81].

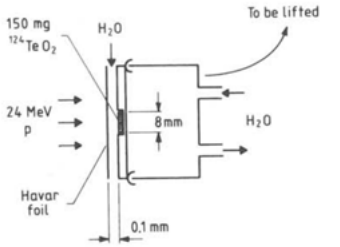

Fig. 5. Simplified sketch of remotely controlled high-current target system used for irradiations of $^{124}TeO_2$ [81].

The ^{124}Te (p, 2n)^{123}I reaction gives high yields of ^{123}I and the dry distillation technique makes the process very convenient. A 1 h irradiation at 30 μA yields easily 120 to 150 mCi ^{123}I. The major limiting factor in the widespread use of this reaction is the level of ^{124}I-impurity, which has considerable influence on the resolution of scintiscans and the dose to the patient [cf. 85, 86]. There has been some controversy regarding the ^{124}I impurity

Table 6. *Summary of methods suggested for the production of "no-carrier added" ^{123}I*

Nuclear reaction	Energy range (MeV)	Theoretical [or experimental] thick target yield (mCi/μAh)	Impurities at EOB (%)	Type of work done	References
Direct methods:					
^{121}Sb(α, 2n)^{123}I	28 → 9		^{124}I(2.8)	Cross sections	73
	25 → 8	[0.15]	^{124}I(<1)	Low current ^{nat}Sb target; wet chemical separation	74
^{nat}Sb(^{3}He, xn)^{123}I	26 → 12			Cross sections	73
^{124}Te(p, 2n)^{123}I	25 → 20	24	^{124}I(0.72)	Cross sections (natural and 91.9% enrichment); low current ^{124}Te-metal target; wet chemical separation	75
	26 → 21	25	^{124}I(0.5–1.2)	Cross sections (91.9 and 99.9% enrichments); ^{124}I-impurity as a function of E_p and target enrichment	76
		[10.6]	^{124}I(0.72)	^{124}Te-metal (99.9% enriched) target for medium currents; wet chemistry	77
	24 →20	20	^{124}I(0.70)	Low current yield measurements; low power density $^{124}TeO_2$ (91.9%) enriched) target; dry distillation of radioiodine	78
	22 →18	[1.3]	^{124}I(0.8)	Medium current ^{124}Te/Al (96% enrichment) pressed target; wet chemistry	79
	26 →21	[8]	^{124}I(<1)	Medium current $^{124}TeO_2$ (96.5% enriched) target; 4π cooling; dry distillation	80
	22.4→20	[3.5]	^{124}I(0.9)	High-current $^{124}TeO_2$ (99.9% enriched) target; 4π cooling; dry distillation; effect of target enrichment on ^{124}I-impurity	81
^{123}Te(p, n)^{123}I	15 → 9	3.2	^{124}I(0.35), ^{130}I (?)	91.5% enriched ^{123}Te-metal target for high currents; medium scale production	82
			^{124}I(0.36), ^{130}I (~1)	Cross sections using 90% enriched ^{123}Te	88
^{122}Te(d, n)^{123}I	14 → 6	[0.75]	^{124}I(<1), ^{130}I(4.5)	$^{122}TeO_2$ (87% enriched) target for medium currents; 2π water cooling	83
	12.7→ 6	1.1 [0.5]	^{124}I(0.08), ^{130}I(1.5)	Cross sections up to 35 MeV using nat. and enriched tellurium; 96.45% enriched $^{122}TeO_2$ target for high currents (up to 30 μA)	84
Indirect method:	^{123}Xe $\xrightarrow[2.08\,h]{EC,\beta^+}$ ^{123}I				
^{122}Te(α, 3n)^{123}Xe	45 → 35	[0.05–0.20]	^{125}I(<0.2)	^{122}Te-metal (>95% enriched) target for high currents; on-line removal of ^{123}Xe; radiation damage effects on target	89
		[0.3]		Development of high current (up to 20 μA) ^{122}Te-Au target	90
	42 → 32	[0.06–0.08]	^{125}I(0.4)	High current (up to 50 μA) ^{122}Te (96% enriched) powder target with large surface area; removal of ^{123}Xe by helium flow	91
	43.2→ 34.5	[0.55]	^{125}I(0.16)	Low current batch process	92
^{123}Te(^{3}He, 3n)^{123}Xe	35.2→ 20.7	[0.71]	^{125}I(0.05)	Yield data using 87.45% enriched ^{123}Te; low current batch process	92

Table 6. (Continued)

Table 6. *Summary of methods suggested for the production of "no-carrier added" ^{123}I*

Nuclear reaction	Energy range (MeV)	Theoretical [or experimental] thick target yield (mCi/μAh)	Impurities at EOB (%)	Type of work done	References
^{124}Te(^{3}He, 4n)^{123}Xe	52.2→ 35.5	[0.79]	^{125}I(0.17)	Yield data using 96.2% enriched ^{124}Te; low current batch process	92
^{127}I(p, 5n)^{123}Xe	65 → 45	24	^{125}I(0.13)	Cross sections	93
	65 → 46	21	^{125}I(0.1)	Cross sections	94
	60 → 48	7	^{125}I(?)	Cross sections up to 90 MeV	95
	58 → 48	10	^{125}I(0.16)	Cross sections up to 160 MeV	96
	58 → 45	[5]	^{125}I(0.12)	Solid I_2 target for low currents: batch process	99, 100
	68 → 45	[8]	^{125}I(0.35)	Molten iodine target for medium currents (<10 μA); on-line removal of ^{123}Xe	103
	58 → 45	[5]	^{125}I(0.13)	Low current NaI target	47, 98, 102
				NaI sol. for medium currents: batch process	101
				High current (<20 μA) flowing liq. target (CH_2I_2/I_2 or LiI/I_2); on-line removal of ^{123}Xe	97, 104 – 106
			^{125}I(<0.2)	High current (<23 μA) molten NaI target; on-line removal of radioxenon	107
^{127}I(d, 6n)^{123}Xe	78 → 64	10 [6 – 8]	^{125}I(0.2)	Cross sections up to 90 MeV; low current NaI target; on-line removal of radioxenon	108 – 110
		[3.5]	^{125}I(0.25)	Medium current (<13 μA) KI (80%) mixed with Sterchamol (20%) target; high helium flow for removal of radioxenon	111
^{127}I(α, x)^{123}Xe	85 → 70	[0.1]	^{125}I(0.86)	Low current NaI target; yield measurements	112
	130 →100	1.6	^{125}I(0.75)	Cross sections up to 160 MeV	113, 114
Cs, Ba, La (p, spall) ^{123}Xe	800 →600	6 – 10	?	High current La/Cu target; batch process	115
			^{125}I(0.4)	Low current CsI target; optimization studies	116
	590 →320	[6 10]	^{125}I(0.44), ^{121}Te(0.25)	Cross sections; low current CsCl, $BaCO_3$, La_2O_3 targets; batch process	117
	660 →600	[6 10]	^{125}I(0.4), ^{121}Te(1.63)	Cross sections; aq. sol. of $CsNO_3$, $Ba(NO_3)_2$ and $La(NO_3)_3$ as low current targets; molten CsCl target for high currents; on-line separation of radioxenon	118
	480 →450	[10]	^{125}I(0.37), ^{121}Te(0.15)	Molten Cs metal target for medium currents (<10 μA); on-line removal of radioxenon	119

levels [75 – 78, 86, 87] associated with the use of ^{124}Te targets of varying isotopic enrichments. However, precise nuclear data measurements at BNL [76] and experimental determination of the level of ^{124}I-impurity at Jülich [81] for various ^{124}Te-enrichments under well-defined high-current production conditions recently resolved the controversy. It is now accepted that the level of ^{124}I impurity cannot be suppressed to < 0.5% even if ^{124}Te is 100% enriched.

In order to overcome the ^{124}I impurity level associated with the (p, 2n) reaction, efforts have been made in recent years to utilize the ^{123}Te(p, n)^{123}I reaction. Using about 90% enriched ^{123}Te it has been shown that the level of ^{124}I impurity (at EOB) is reduced to 0.35% [82]. There are, however, three drawbacks of this method: (a) Enrichments of ^{123}Te higher than 90% have prohibitive costs, (b) the yield of ^{123}I is lower than that in the case of the (p, 2n) reaction, (c) in addition to ^{124}I impurity,

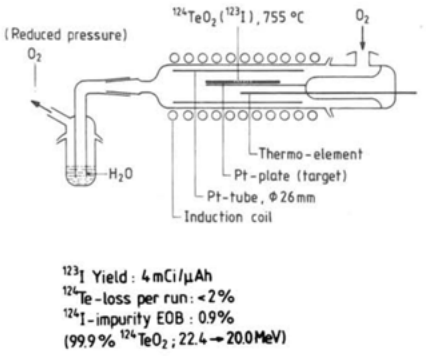

Fig. 6. Sketch of quartz apparatus for dry distillation of ^{123}I using induction heating [81].

the radioisotope ^{130}I (~ 1%) is also formed [88].

Parallel to the (p, n) and (p, 2n) reactions mentioned above, the $^{122}Te(d, n)^{123}I$ reaction has also been investigated [cf. 83, 84]. Using 96.45% enriched ^{122}Te it has been shown [84] that the levels of ^{124}I and ^{130}I impurities (at EOB) amount to < 0.1 and 1.5%, respectively. These levels can be reduced further if ~ 99% enriched ^{122}Te (whose price is still reasonable) is used. The major drawback of this reaction, however, is the low yield.

A comparison of the three direct methods of production has been recently given [84]. It was concluded that the significantly higher yield of the (p, 2n) process, as compared to the (p, n) and (d, n) processes, may justify the use of that reaction for large scale production of ^{123}I, especially for those medical applications which are completed within a few hours.

A summary of the indirect methods [89–119] used to produce ^{123}Xe precursor for subsequent formation of the ^{123}I daughter is also given in Table 6. This precursor method of production leads to high-purity product, the major impurity being ^{125}I ($t_{1/2}$ = 60 d). The yield of ^{123}I and the level of ^{125}I impurity are dependent on the decay time of ^{123}Xe chosen. The optimum decay time is about 6 h and the yield and impurity data given in Table 6 generally correspond to this value.

The ^3He- and α-particle induced nuclear reactions on tellurium isotopes (^{122}Te, ^{123}Te, ^{124}Te) have been well investigated [cf. 89–92], and a high-current Te-Au target material has been developed which is capable of withstanding nominal beam currents of 20 μA [90]. The removal of ^{123}Xe was done both on-line by helium flow, and as a batch process. The cross sections and hence batch yields achieved via these reactions were, however, too low (6–8 mCi). These reactions are therefore no longer used for production.

The most commonly used process for the indirect production of ^{123}I is the $^{127}I(p, 5n)^{123}Xe$ reaction. The excitation function of this reaction has been measured by several groups [cf. 93–96] and the results are summarized

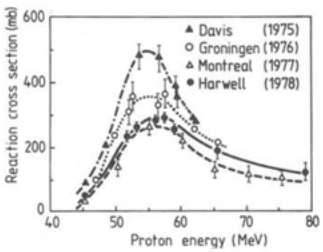

Fig. 7. Excitation function of the $^{127}I(p, 5n)^{123}Xe$ reaction measured by different groups [93–96].

in Fig. 7. There are considerable discrepancies in the region of the maximum of the excitation function. The data from Davis [93] appear to be too high. The difference in the theoretically expected integrated yield for a given target thickness, however, does not exceed 35%. The $^{127}I(d, 6n)^{123}Xe$ reaction is similar to the (p, 5n) reaction and has been used extensively in our laboratory [cf. 108–110]. The $^{127}I(\alpha, x)^{123}Xe$-process [cf. 112–114] has not found any practical application.

For large scale production of ^{123}I via the (p, 5n) or (d, 6n) process, several target systems have been used and radioxenon is generally removed on-line. Some of the important systems are high He-flow NaI or KI solid target [111], molten I_2, or NaI target [103, 107], flowing-loop liquid (CH_2I_2/I_2 or LiI/I_2) target [97, 104–106]. A simplified sketch of the system used at Davis is given in Fig. 8. The radioxenon is frozen and allowed to decay for 6 h. Thereafter it is pumped out. Radioiodine formed adheres to the walls of the vessel and is removed by introducing water with some reducing agent.

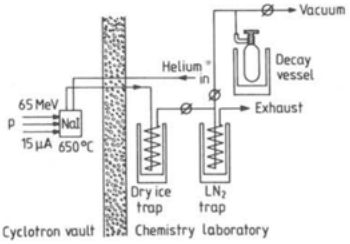

Fig. 8. Simplified sketch of the system used for the production and on-line removal of radioxenon from a molten NaI target at Davis [107].

In addition to the on-line system for the removal of radioxenon, irradiation of a NaI pellet or NaI solution followed by batch removal of radioxenon has also been successfully applied.

It is worth pointing out that the corrosive nature of the target materials used causes special problems in target construction. Furthermore, under the impact of high radiation doses most of the target materials undergo severe

radiation damage effects. The yields of radioxenon removal therefore decrease appreciably with increasing radiation doses. Under high-current production conditions ^{123}I yields of 3–5 mCi/μAh are obtained. Batch yields of up to several hundred mCi have been reported.

In addition to the medium energy reactions discussed above, ^{123}Xe has also been obtained by high energy spallation of Cs, Ba and La using the high-energy machines LAMPF [cf. 115, 116], SIN [cf. 117], JINR [cf. 118] and TRIUMF [cf. 119]. Here also some high-current targets using materials such as La/Cu, molten CsCl and molten Cs have been developed and separation of radioxenon has been effected both on-line and as a batch process. The main advantage of this process is that production of ^{123}Xe can generally follow in a parasitic position, i.e. parallel to the high-energy physics experiments which generally require only a small fraction of the available beam intensity. The major disadvantage of the process was considered until recently to be the ^{125}I impurity. Recent nuclear data measurements and optimization studies [cf. 117–119], however, have shown that the level of the ^{125}I impurity can be reduced to ~ 0.4% of the ^{123}I activity (at EOB). Some contribution from ^{121}Te is also present.

The above discussion leads to the conclusion that the two most important processes for the production of ^{123}I, according to the present state of knowledge, involve the ^{124}Te(p, 2n)^{123}I reaction and the ^{123}Xe → ^{123}I precursor method using the (p, 5n), (d, 6n) or spallation reactions for ^{123}Xe production. The main limiting factor in the use of the former reaction is the ^{124}I-impurity. In the latter process, ^{123}I is produced using a medium or high-energy machine and therefore the production cost is rather high.

Astatine-211

Methods used for the production of this radioisotope have recently been reviewed [cf. 120]. Similar to other radiohalogens, it can be produced via two routes, *viz.* directly and via the decay of its precursor ^{211}Rn ($t_{1/2}$ = 14.6 h). In comparison to ^{75,77}Br and ^{123}I, however, the number of nuclear reactions investigated is relatively small, and a summary of the suggested methods [cf. 121–125] is given in Table 7.

For the direct production of ^{211}At, two processes have been considered: (i) ^{3}He-, α-particle and heavy-ion induced reactions on bismuth, (ii) high energy proton induced spallation of thorium and uranium. The ^{3}He- and heavy-ion induced reactions on bismuth [cf. 121, 123] give low yields. Furthermore, ^{211}At is contaminated with several other isotopes of astatine. These processes are therefore not suitable for production purposes. The ^{209}Bi(α, 2n)^{211}At reaction, on the other hand, leads to a relatively high-yield and high-purity product. When α-energies from 28→0 MeV are used the impurity of ^{210}At is almost negligible. This reaction has therefore been commonly used for large scale production of ^{211}At. For chemical separation of the desired product, both the dry distillation technique and wet chemical methods have been used [120, 126–128] and batch yields of up to 50 mCi have been reported [120, 127, 129]. The spallation of thorium and uranium leads to radioastatine, but several fission products are simultaneously formed. Using a thermochromatographic method, it was possible at JINR [124] to obtain radioastatine in a batch yield of about 5 mCi. Though the product was free from other elements, it was a mixture of various astatine isotopes.

Table 7. *Summary of methods used for the production of* ^{211}At

Nuclear reaction	Energy range (MeV)	Theoretical [or experimental] thick target yield (mCi/μAh)	Impurities at EOB (%)	Type of work done	References
Direct methods:					
^{209}Bi(^{3}He, n)^{211}At	32 → 25	$< 1 \times 10^{-3}$	Large contamination from ^{210}At and ^{209}At	Cross sections	121
^{209}Bi(α, 2n)^{211}At	28 → 0	0.5 [0.4]	^{210}At (< 1)	Cross sections	122
				High current Bi-metal target; dry distillation and wet chemistry	120, 126–129
^{209}Bi(Kr, x)At	500		Mixture of astatine isotopes	Cross sections	123
^{232}Th, ^{238}U(p, spall)At	660	[2 for radioastatine]	Mixture of astatine isotopes	Yields; thermochromatographic separation	124
Indirect methods:					
^{232}Th(p, spall)Rn → At	660	[0.2 for radioradon]	Mixture of radon isotopes	Yields; thermochromatography and distillation	124
^{209}Bi(Ar, x)Rn → At	450		Mixture of radon isotopes	Cross sections	123
^{209}Bi(^{7}Li, 5n)^{211}Rn → At	60 → 38	0.2	^{210}At(0.04)	Cross sections; degassing technique	125

The indirect method of ^{211}At-production, i.e. via the decay of its precursor ^{211}Rn, has not been investigated in detail. Both the spallation of ^{232}Th [124] and the heavy-ion induced reactions on bismuth [123] give a mixture of radon isotopes; the subsequent yield of ^{211}At is rather low. Recent cross section studies [125] on the ^{209}Bi(^{7}Li, 5n)^{211}Rn reaction have shown that ^{211}At of very high purity can be obtained using this reaction. However, since ^{7}Li-beams are seldom available at medical cyclotrons, this reaction is of relatively little interest. The main choice for the production of ^{211}At therefore lies in the ^{209}Bi(α, 2n)^{211}At reaction.

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Appendix III

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Cyclotron Production of Generator Radionuclides

By S. M. QAIM, Institut für Chemie 1 (Nuklearchemie), Kernforschungsanlage Jülich GmbH, D-5170 Jülich, FRG

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Generator radionuclides / Cyclotron production / Nuclear reaction cross section / Excitation function / Targetry / Thick target yield / Radiochemical separation / Quality control

Summary

Some of the cyclotron produced generator systems are reviewed. The various useful or potentially useful nuclear processes leading to the formation of the parent nuclides are given and the status of nuclear data is discussed. A brief review of the common production routes involving high-current targetry and chemical separation procedures is given. Some of the quality control measures are discussed.

Introduction

Radionuclide generators have contributed appreciably to the advancement of diagnostic nuclear medicine and other tracer studies. Through the supply of a long-lived parent, from which a short-lived daughter radioisotope can be milked off periodically at the site of application, it has become possible to use short-lived radioisotopes even in areas far from a reactor or a cyclotron.

A large number of potentially useful radionuclide generator systems have been suggested and several reviews have been published [cf. refs. 1–9]. The reactor produced parent radioisotopes lead to γ-emitting daughter nuclides which are detected in nuclear medicine either using a γ-camera or, in suitable cases, via single photon emission tomography (SPECT). The cyclotron produced systems, on the other hand, lead not only to γ-emitters but in several cases also to β^+ emitters which find application in positron emission tomography (PET). A list of cyclotron produced generator radioisotopes together with the decay properties of both the parent and the daughter nuclides is given in Table 1. The decay data are generally well known. Only in the case of ^{52m}Mn the β^+ branching is not known accurately and for ^{82}Rb there is uncertainty in the intensity of the 776 keV γ-ray. Some of the parent radioisotopes (for example ^{52}Fe) are used more commonly as a tracer rather than in the generator form. Several of the known or potential applications of the daughter isotopes are also outlined. Although the list given in Table 1 is relatively long, and several other nuclides are also potentially useful, the choice lies presently mainly on a few systems like ^{68}Ge–^{68}Ga, ^{81}Rb–^{81m}Kr, ^{82}Sr–^{82}Rb, etc. where the radiochemical and radiopharmaceutical problems relevant to the separation of the daughter radioisotopes have been solved. The γ-emitting ultra short-lived ^{81m}Kr is mainly used for ventilation and perfusion studies in the lung. The radioisotopes ^{82}Rb and ^{68}Ga, on the other hand, find application in PET, the former for myocardial perfusion study and the latter for measuring blood-brain barrier integrity as well as for tumor localisation. Furthermore, the ^{68}Ge-^{68}Ga generator is widely used for attenuation correction of positron tomographs. This review deals with the cyclotron production of the parent activities. So far any detailed review of this aspect has not been given. The loading of generator columns, elution of daughter activities and quality control have been discussed recently [5, 9] and are also the subject of another paper in this Seminar [10].

The production of radioisotopes using a cyclotron demands a knowledge of nuclear reaction cross-section data, development of high-current targets, chemical separation of products, recovery of the target material (if isotopically enriched), remote control and automation, etc. [cf. ref. 11]. Several of these aspects are discussed below. In general, the cyclotron production of radioisotopes involves a more sophisticated technology than the reactor production, but the cyclotron radioisotopes are more versatile and of high specific activity. This results in lesser stringent demands on the preparation of generator columns since the breakthrough problems are not as severe as in the case of (n, γ) products.

Nuclear reaction cross sections

The role of nuclear reaction cross-section data in optimisation of production methods, especially with respect to the yield and purity of the desired product, was discussed in detail [12]. A large number of nuclear reactions may lead to the formation of a radioisotope. However, the choice for large scale production generally lies on a few selected routes. Some of the important considerations include the type and energy of the particles accelerated at a given cyclotron [cf. 13], and the enrichment, cost and availability of the target material [cf. 14]. As an example, the excitation functions of various nuclear processes leading to the formation of ^{81}Rb (a commonly used generator parent), are shown in Fig. 1. This radioisotope can be produced via ^{82}Kr(p, 2n)^{81}Rb, ^{79}Br(α, 2n)^{81}Rb and ^{81}Br(^{3}He, 3n)^{81}Rb reactions at a medium-sized cyclotron, or using the ^{85}Rb(p, p4n)^{81}Rb process at a higher energy machine. For large scale routine production, however, the ^{82}Kr(p, 2n)^{81}Rb reaction is the method of choice, although its excitation function is not known accurately and the target material needed in high enrichment is rather expensive, demanding thereby a good recovery system to be able to use it in subsequent production runs.

Table 1. Some cyclotron-produced generator radionuclides

Generator nuclides	Decay characteristics of parent[a]			Decay characteristics of daughter[a]			Application of the daughter
	$T_{1/2}$	Mode of decay	Principal γ-rays E_γ in keV, I_γ (%)	$T_{1/2}$	Mode of decay	Principal γ-rays E_γ in keV, I_γ (%)	
^{44}Ti - ^{44}Sc	48.2 y	EC (100)	68 (88) 78 (94)	3.9 h	EC (5) β^+ (95)	511 (190) 1157 (99.9)	Study of bone disease
^{52}Fe - ^{52m}Mn	8.3 h	EC (43.5) β^+ (56.5)	169 (99.2) 511 (113)	21.1 m	EC+β^+ (98.3) IT (1.7)	511 (< 196) 1434 (98.2)	Myocardial perfusion
^{62}Zn - ^{62}Cu	9.2 h	EC (93.1) β^+ (6.9)	409 (25) 597 (24)	9.7 m	EC (2.2) β^+ (97.8)	511 (195.6)	Biological studies
^{68}Ge - ^{68}Ga	271 d[b]	EC (100)	none	68.3 m	EC (10) β^+ (90)	511 (180) 1077 (3)	Blood-brain barrier; tumor localisation
^{72}Se - ^{72}As	8.4 d	EC (100)	46 (57.3)	26.0 h	EC (23) β^+ (77)	511 (154) 834 (80)	Toxicological study
^{81}Rb - ^{81m}Kr	4.6 h	EC (73) β^+ (27)	446 (19) 511 (54)	13.1 s	IT (100)	190 (67)	Lung ventilation; perfusion
^{82}Sr - ^{82}Rb	25.0 d	EC (100)	none	1.3 m	EC (4) β^+ (96)	511 (192) 776 (15.5)[b]	Myocardial perfusion
^{87}Y - ^{87m}Sr	80.3 h	EC (99.8) β^+ (0.2)	485 (92)	2.8 h	EC (0.3) IT (99.7)	388 (82)	Bone scanning; calcium metabolism
^{113}Sn - ^{113m}In	115.1 d	EC (100)	255 (1.8)	1.7 h	IT (100)	392 (64)	Various radio-pharmaceuticals
^{118}Te - ^{118}Sb	6.0 d	EC (100)	none	3.5 m	EC (24) β^+ (76)	511 (152)	First-pass angiography
^{122}Xe - ^{122}I	20.1 h	EC (100)	350 (8)	3.6 m	EC (23) β^+ (77)	511 (154) 564 (18)	Various radio-pharmaceuticals
^{128}Ba - ^{128}Cs	2.4 d	EC (100)	273 (14.5)	3.6 m	EC (39) β^+ (61)	443 (25.8) 511 (132)	Myocardial perfusion
^{178}W - ^{178}Ta	21.5 d	EC (100)	none	9.3 m	EC (98.9) β^+ (1.1)	93 (6.6) ~ 57 (95)[c]	Left ventricular function
^{195m}Hg - ^{195m}Au	40.0 h	EC (49) IT (51)	560 (8.6)	30.6 s	IT (100)	262 (67)	First-pass angiography

[a] Decay data taken from Table of Isotopes (Lederer and Shirley, eds.), 7th Edition, John Wiley, New York (1978), unless otherwise stated.
[b] This is a more recent value reported from the National Physical Laboratory, England.
[c] K X-rays, demanding use of a special camera.

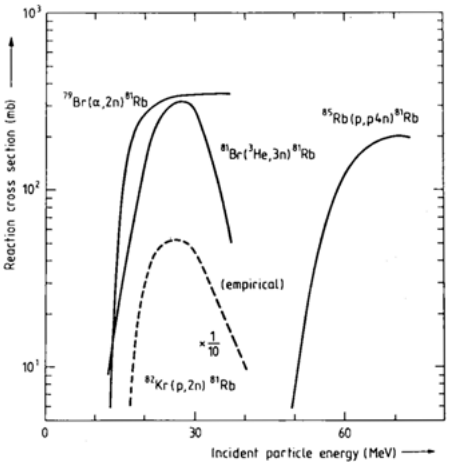

Fig. 1. Excitation functions of ^{79}Br(α, 2n)^{81}Rb, ^{81}Br(^{3}He, 3n)^{81}Rb and ^{85}Rb(p, p4n)^{81}Rb reactions [refs. 33, 36]. The curve for the ^{82}Kr(p, 2n)^{81}Rb reaction (notice the difference in scale) was constructed empirically using the method described in ref. [26].

Several nuclear reactions which can possibly be used for the production of generator radioisotopes mentioned above are listed in Table 2 [cf. refs. 15–54]. In addition to the investigated energy ranges some characteristics of the excitation functions (like the energy at which the cross section maximum occurs and the respective cross section) are described and the relevant references given. The status of the cross-section data according to the criteria described earlier [12] is also given. Even somewhat exotic reactions induced by ^{3}He or α-particles at energies above 100 MeV are included since the experimental data constitute a good fundamental base for developing systematics. In suggesting the potentially useful reactions, however, three types of cyclotrons were kept in view: (a) compact cyclotron, accelerating p, d,

Table 2. Nuclear processes for the cyclotron production of some generator radionuclide parents

Nuclide	Nuclear process	Natural abundance of target isotope (%)	Q-value of reaction (MeV)	Investigated energy range (MeV)	Maximum of excitation function at energy (MeV)	Cross section at maximum (mb)	Status of cross-section data	Ref.
^{44}Ti	^{45}Sc(p, 2n)^{44}Ti	100	−12.4	15 − 85	32	65	good	15
	^{44}Ca(^{3}He, 3n)^{44}Ti	2.08	−13.2					
	^{nat}Ti(α, 2pxn)^{44}Ti			43 − 170	170	3.3	good	16
	^{51}V(p, spall)^{44}Ti	~100	−70.4	200	average yield		poor	5
^{52}Fe	^{55}Mn(p, 4n)^{52}Fe	100	−34.4	65	average yield		poor	17
	^{59}Co(d, 2p7n)^{52}Fe	100	−71.8	73 − 85	> 85	> 0.1	poor	18
	^{52}Cr(^{3}He, 3n)^{52}Fe	83.5	−16.4	10 − 45	34	5	fair	19,20
	^{50}Cr(α, n)^{52}Fe	4.35	−15.6	20 − 90	28	1	fair	19,21,22
	^{nat}Cu(^{3}He, spall)^{52}Fe			258 − 910		0.2 − 0.4	fair	23
	Ni(p, spall)^{52}Fe			800		1.5	fair	24
	As(p, spall)^{52}Fe			593		0.04	fair	25
^{62}Zn	^{63}Cu(p, 2n)^{62}Zn	69.1	−13.3	15 − 100	25	110	good	26,52,53
	^{61}Ni(^{3}He, 2n)^{62}Zn	1.16	− 4.3					
	^{62}Ni(^{3}He, 3n)^{62}Zn	3.71	−14.9					
	^{60}Ni(α, 2n)^{62}Zn	26.4	−17.1	12 − 38	31	140	good	26,27
	^{nat}Ni(α, xn)^{62}Zn			17 − 122	30	36	good	16
	^{nat}Zn(γ, xn)^{62}Zn			e⁻ 30 − 60	average yield		poor	28
	^{nat}Cu(^{3}He, spall)^{62}Zn			258 − 910		1.2 − 2.7	fair	23
	RbBr(p, spall)^{62}Zn			800		2	fair	29
	Rb, Br, As(p, spall)^{62}Zn			593		0.3 − 1.17	fair	25
^{68}Ge	^{69}Ga(p, 2n)^{68}Ge	60	−11.5	13 − 55	19	500	good	26
	^{71}Ga(p, 4n)^{68}Ge	40	−28.4	36 − 56	43	140	good	26
	^{69}Ga(d, 3n)^{68}Ge	60	−13.7	14 − 32	28	550	good	26
	^{nat}Ge(p, pxn)^{68}Ge			24 − 64	37	100	good	30
	^{67}Zn(^{3}He, 2n)^{68}Ge	4.1	− 2.4					
	^{68}Zn(^{3}He, 3n)^{68}Ge	18.6	−12.6					
	^{nat}Zn(α, xn)^{68}Ge			19 − 35	32	150	good	50
	RbBr(p, spall)^{68}Ge			800		19	fair	29
	Y, Rb, Br, As(p, spall)^{68}Ge			593		6.7 − 11.1	fair	25
^{72}Se	^{75}As(p, 4n)^{72}Se	100	−31.7	35 − 50	~ 50	120	fair	31
	^{nat}Ge(^{3}He, xn)^{72}Se			20 − 40	35	70	fair	31,32
	^{70}Ge(α, 2n)^{72}Se	20.7	−17.9	20 − 40	33	320	fair	26,32,51
	^{nat}Ge(α, xn)^{72}Se			20 − 40	33	70	fair	31
	RbBr(p, spall)^{72}Se			800		12	fair	29
	Y, Rb, Br, As(p, spall)^{72}Se			593		1.4 − 6.0	fair	25
^{81}Rb	^{85}Rb(p, p4n)^{81}Rb	72.17	−39.0	47 − 70	70	200	fair	33
	^{82}Kr(p, 2n)^{81}Rb	11.6	−14.0					
	^{80}Kr(d, n)^{81}Rb	2.25	+ 2.6					
	^{nat}Kr(p, xn)^{81}Rb			12 − 45	27	yield values	fair	34,35
	^{nat}Br(^{3}He, xn)^{81}Rb			12 − 37	27	350	fair	36
	^{79}Br(α, 2n)^{81}Rb	50.69	−14.4	13 − 38	30	380	fair	36
^{82}Sr	^{85}Rb(p, 4n)^{82}Sr	72.17	−31.9	34 − 68	50	200	good	33
	^{82}Kr(^{3}He, 3n)^{82}Sr	11.6	−14.6	15 − 36		} measurements		37
	^{nat}Kr(^{3}He, xn)^{82}Sr			15 − 36		} in progress		
	^{80}Kr(α, 2n)^{82}Sr	2.25	−16.3					
	Rb, Mo(p, spall)^{82}Sr			800		2.1; 24.5	fair	29,38
	Rb, Y(p, spall)^{82}Sr			593		2.6; 19.7	fair	25
^{87}Y	^{89}Y(p, p2n)^{87}Y	100	−20.8	540 − 593		53.3	fair	25
	^{87}Sr(p, n)^{87}Y	7.0	− 2.7	3 − 7	> 7	>500	fair	26
	^{88}Sr(p, 2n)^{87}Y	82.6	−13.8	15 − 33	26	1200	good	26
	^{86}Sr(d, n)^{87}Y	9.9	+ 3.5					
	^{87}Rb(^{3}He, 3n)^{87m}Y	27.83	−10.9	12 − 37	18	85	fair	39
	^{85}Rb(α, 2n)^{87m}Y	72.17	−12.9	15 − 40	26	800	good	26,39
^{113}Sn*	^{113}In(p, n)^{113}Sn	4.3	− 1.8					
	^{115}In(p, 3n)^{113}Sn	95.7	−18.1					
	^{115}In(d, 2n)^{113}Sn	4.3	− 4.0					
	^{112}Cd(^{3}He, 2n)^{113}Sn	24.0	− 3.5					
	^{113}Cd(^{3}He, 3n)^{113}Sn	12.3	−10.0					
	^{111}Cd(α, 2n)^{113}Sn	12.8	−14.7					
	^{nat}In(^{3}He, pxn)^{113}Sn			20 − 115	55	850	good	40
	^{nat}In(α, pxn)^{113}Sn			40 − 135	85	700	good	40
	^{nat}Cd(^{3}He, xn)^{113}Sn			5 − 120	38	400	fair	40
	^{nat}Cd(α, xn)^{113}Sn			10 − 140	55	270	fair	40

Table 2 (Continued)

Nuclide	Nuclear process	Natural abundance of target isotope (%)	Q-value of reaction (MeV)	Investigated energy range (MeV)	Maximum of excitation function at energy (MeV)	Cross section at maximum (mb)	Status of cross-section data	Ref.
^{118}Te	^{121}Sb(p,4n)^{118}Te	57.3	−27.1		44	700 (calculated)	poor	41
	^{123}Sb(p,6n)^{118}Te	42.7						
	^{117}Sn(^{3}He, 2n)^{118}Te	7.6	− 4.1					
	^{118}Sn(^{3}He,3n)^{118}Te	24.1	−13.4					
	^{116}Sn(α,2n)^{118}Te	14.4	−17.8					
^{122}Xe	^{127}I(p,6n)^{122}Xe	100	−45.2	60− 85	72	115	good	42,43
	^{127}I(d,7n)^{122}Xe	100	−47.4	55− 90	85	200	good	44
	^{122}Te(^{3}He,3n)^{122}Xe	2.4	−14.7					
	Cs,Ba,La(p,spall)^{122}Xe			320−660		2.6 − 25.0	good	45,46
^{128}Ba	^{133}Cs(p,6n)^{128}Ba	100	−44.4	48− 68	65	290	fair	47
	^{128}Xe(^{3}He,3n)^{128}Ba	1.9	−14.3					
^{178}W	^{181}Ta(p,4n)^{178}W	~100	−23.0	30− 84	36	780	good	26
	^{177}Hf(^{3}He,2n)^{178}W	18.5	− 3.7					
	^{178}Hf(^{3}He,3n)^{178}W	27.2	−11.3					
	^{176}Hf(α,2n)^{178}W	5.2	−17.9					
^{195m}Hg	^{197}Au(p,3n)^{195m}Hg	100	−17.9	20− 42	27	yield values	fair	48
	^{197}Au(d,4n)^{195m}Hg	100	−20.2	33− 80	35	600	fair	49
	^{194}Pt(^{3}He,2n)^{195m}Hg	32.9	− 5.8					
	^{192}Pt(α,n)^{195m}Hg	0.78	−11.8					

* This radioisotope is produced generally via an (n,γ) reaction in a nuclear reactor. The specific activity is, however, low.

^{3}He and ^{4}He up to $E \leqslant 40$ MeV, (b) single particle cyclotron with $E_p \leqslant 70$ MeV, (c) high-energy single particle cyclotron or accelerator with $E_p \geqslant 200$ MeV. For utilizing many of the potential reactions highly enriched and expensive target material is mandatory. If the feasibility of several of those processes for production could be demonstrated, there will be need for detailed excitation function measurements. In general if protons of suitable energy are available their use is to be preferred since the yields are generally higher. However, in several cases (^{3}He, xn) reactions are also quite useful.

Cyclotrons are generally used for production of short-lived radioisotopes. As far as generator systems are concerned, the best application of medium-sized cyclotrons relates to the formation of ^{52}Fe-^{52m}Mn, ^{81}Rb-^{81m}Kr and ^{195m}Hg-^{195m}Au. In the case of long-lived parents like ^{68}Ge and ^{82}Sr, although nuclear processes like ^{69}Ga(p, 2n)^{68}Ge and ^{82}Kr(^{3}He, 3n)^{82}Sr appear to have appreciable cross sections, the production using a medium-sized cyclotron is very expensive since long irradiations are needed. The thick target yields of ^{82}Sr via various nuclear processes [cf. refs. 33, 37, 54, 55] are given in Table 3. The yield in the spallation process is not the highest; nonetheless, this production route is preferred since high-current long parasitic irradiations result in high ^{82}Sr batch yields. In the spallation process usually elements of natural isotopic composition are used as targets. This results generally in higher isotopic impurity (see below). It should be mentioned that if long parasitic irradiations could be performed at medium-energy cyclotrons as well, several routes would be advantageous.

Table 3. Thick target yields of ^{82}Sr

Nuclear reaction	Energy range (MeV)	Yield (KBq/μAh)	Ref.
^{85}Rb(p,4n)^{82}Sr	60 → 40	14800[a]	33
^{nat}Kr(^{3}He,xn)^{82}Sr	34 → 20	104[a,b]	37
^{nat}Kr(α,xn)^{82}Sr	35 → 25	37	54
Mo(p,spall)^{82}Sr	800	~3700[c]	55

a Calculated from the excitation function.
b Yield can be increased by a factor of 7 if highly enriched ^{82}Kr is used as target material.
c High-current long parasitic irradiations lead to high batch yields.

Targetry and radiochemical separations

A summary of the methods commonly used for the production of various generator parent radioisotopes is given in Table 4 [cf. refs. 55−71]. In general medium to large scale production of all the radioisotopes has been achieved. ^{113}Sn is, however, produced more often via an (n,γ) reaction in a nuclear reactor. As expected, more effort has been devoted to the production of systems where practical usefulness has already been demonstrated.

A consideration of the energy ranges used shows that several of the radioisotopes are produced using medium-sized cyclotrons, but some of them demand a 70 MeV proton machine. In special cases the spallation process has proved to be quite advantageous.

The experimental thick target yields under high-current production conditions are also given in Table 4. In

Table 4. Summary of common methods used for the production of cyclotron-based generator radionuclide parents

Radio isotope	Nuclear process	Energy range used (MeV)	Experimental thick target yield (KBq/μAh)	Target	Chemical separation method	Impurities (%)	Ref.
^{44}Ti	^{51}V(p,spall)^{44}Ti	200	2220	V	ion exchange		5,56
	^{55}Mn(p,4n)^{52}Fe	70 → 50	3600	Mn	ion exchange	^{55}Fe (0.7)	57
	^{52}Cr(^{3}He,3n)^{52}Fe	45 → 10	1850	Cr	solvent extraction	^{55}Fe (0.001)	58
	^{nat}Ni(p,spall)^{52}Fe	800, 450	24000	Ni	ion exchange	^{55}Fe (3)	58
^{62}Zn	^{63}Cu(p,2n)^{62}Zn	22 → 15	85000	Cu	ion exchange		59
^{68}Ge	^{69}Ga(p,2n)^{68}Ge	22 → 13	740	Ga_2O_3 Ga_4Ni	ion exchange; solvent extraction	^{57}Co (0.001)	60,61
	Rb,Br,As(p,spall)^{68}Ge	800, 500	74	RbBr	distillation; solvent extraction	^{71}Ge (3)	62,63
^{72}Se	^{70}Ge(α,2n)^{72}Se	40 → 30	600	Ge	precipitation; ion exchange		5,51
^{81}Rb	^{82}Kr(p,2n)^{81}Rb	23 → 15	166500	Kr gas	target wash		5,6,9,34,35
^{82}Sr	Mo(p,spall)^{82}Sr	800	~3700	Mo	ion exchange	^{85}Sr (100)*	55,64
^{87}Y	^{88}Sr(p,2n)^{87}Y	26 → 20	44400	SrO : $SrCl_2$	extraction chromatography	^{88}Sr (0.5)	65
^{113}Sn	^{115}In(^{3}He,p4n)^{113}Sn	110 → 60	1100	In	dry distillation	^{117m}Sn (1.5)	40
^{118}Te	^{121}Sb(p,4n)^{118}Te	58 → 35	~11000	Sb	distillation	^{119}Te (125)*, ^{121}Te (6)	57
^{122}Xe	^{127}I(p,6n)^{122}Xe	65 → 43	137000	molten NaI	batch or on-line gas removal	^{125}Xe (250)*	57,66
^{128}Ba	^{133}Cs(p,6n)^{128}Ba	67 → 54	111000	CsCl	ion exchange	^{131}Ba (11)	47,67
^{178}W	^{181}Ta(p,4n)^{178}W	40 → 32	2035	Ta	ion exchange		68,69
^{195m}Hg	^{197}Au(p,3n)^{195m}Hg	34 → 26	170200	Au	dry distillation	^{197m}Hg (3.5)	9,48,70,71

* The amount of this impurity is relative to 100 for the desired radioisotope.

several cases the yield/μAh is low. Nonetheless, sufficiently high batch yields have been achieved through sophisticated high-current targetry.

The target materials used for production purposes are also listed in Table 4. In general metals with high melting points have been commonly used but some alloys, oxides and mixtures of compounds have also found application. Diverse target systems in solid, molten and gaseous forms have been developed. Whereas for the molten and gaseous systems only extracted beams have been used, the solid targets could be irradiated both in internal and external beams. A typical target used for the production of ^{68}Ge [cf. ref. 61] is shown in Fig. 2. The target material consists of an alloy of gallium (Ga_4Ni) and irradiations are done for about 60 h with 20 MeV protons at beam currents of about 45 μA. The target is cooled at the back by a water flow and at the front by a stream of helium. For production via the spallation process, target systems capable of withstanding 800 MeV proton beams of up to 500 μA have been developed.

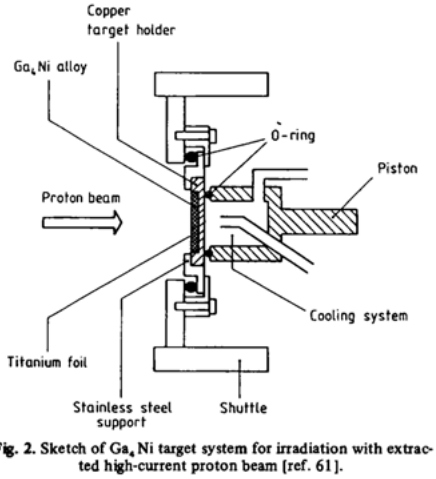

Fig. 2. Sketch of Ga_4Ni target system for irradiation with extracted high-current proton beam [ref. 61].

The physico-chemical methods used for the separation of the radionuclides, generally in no-carrier-added forms, are listed in Table 4. In the case of a gas target, like the one used for the production of ^{81}Rb, removal of the target gas after the end of the irradiation and a target wash either in static or rotational mode leads to a sufficiently high recovery yield of the desired radioisotope. The radioactive rare gases, like the isotopes of xenon, are removed from the molten targets by a stream of helium. A simplified sketch of the system used for the on-line removal of ^{122}Xe [cf. ref. 66] is shown in Fig. 3. The radioxenon swept is frozen and used subsequently for the preparation of the generator. As an alternative, irradiation of a NaI pellet followed by batch removal of radioxenon has also been applied [cf. ref. 57]. Some of the metals having high vapour pressures (for example mercury) are separated by dry distillation [cf. 70]. Radiotin, on the other hand, is separated from irradiated In by a stream of Cl_2 since $^{113}SnCl_4$ has a very high vapour pressure (cf. 40).

Often several step wet radiochemical methods of separation are mandatory, especially when the target and the product have very similar vapour pressures. The techniques

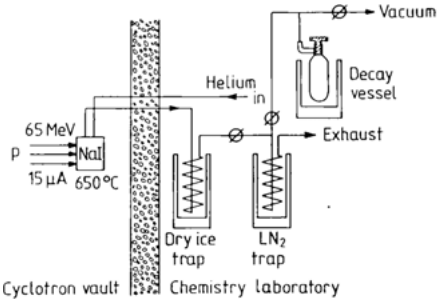

Fig. 3. Simplified sketch of the system used for the production and on-line removal of radioxenon from a molten NaI target at Davis [cf. ref. 66].

commonly used include distillation, solvent extraction, ion exchange chromatography and extraction chromatography. In many cases a combination of various techniques is essential to obtain good separations from non-isotopic impurities. The demand on radiochemical work generally increases with the increasing energy of the incident particle since the number of products also increases. For the separation of radioisotopes produced in the spallation process, for example, extensive chemical steps are necessary. Fig. 4 gives a flow-sheet of the procedures involved in the separation of ^{82}Sr from Mo irradiated with 800 MeV protons [cf. ref. 55].

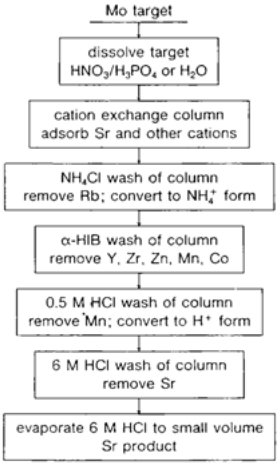

Fig. 4. Flow sheet for the separation of ^{82}Sr from Mo irradiated with 800 MeV protons [ref. 55].

The large scale production of radioisotopes involves work with high-level of radioactivity. Evidently the various unit operations (irradiation, removal of the target, chemical processing etc.) demand remote control or automation. Furthermore, the chemical processing has to be done in lead cells or behind a lead shield. This is particularly true for the 511 keV annihilation radiation of β^+ emitters. Attempts are therefore always underway to simplify the procedures as far as possible.

Quality control

In general quality control measures for radionuclidic, radiochemical and chemical purity are necessary [cf. ref. 72]. The radionuclidic purity of a product is usually checked via high-resolution γ-ray spectroscopy. However, in the case of pure β^+ emitters (having no characteristic γ-rays) an unambiguous identification is difficult unless a check of half-life is performed. The impurities associated with the production methods for various generator radioisotopes, if reported, are given in Table 4. Apparently, the spallation process leads to higher impurities. The radiochemical purity, i.e. the existence of the radioisotope in a well defined radiochemical form, is of considerable importance while loading a generator column since subsequent elution characteristics of the daughter are often strongly dependent on the state of the parent. The chemical purity of the parent, i.e. the absence of inactive isotopic and non-isotopic impurities, is also important.

It should be mentioned that in generator systems the quality control of the daughter is much more important than that of the parent since the daughter finds direct application. Besides the quality measures described above sterility and apyrogenicity are also often required. This demands considerable radiochemical and chemical efforts in the design and use of generator columns.

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Appendix IV

Radiochim. Acta **89**, 297–302 (2001)

Therapeutic radionuclides and nuclear data

By S. M. Qaim*

Institut für Nuklearchemie, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

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Therapeutic radionuclide / Decay data / Corpuscular radiation / Endoradiotherapy / Radiation dose / Production data

Summary. The nuclear data required for the production and endotherapeutic application of radionuclides are outlined. The three types of therapeutic radionuclides, viz. β^--emitters, α-emitters and Auger electron emitters, are considered and the role of some β^+-emitters in therapy planning is discussed. The status of available data is reviewed.

1. Introduction

Radiation therapy has gained an important place in medicine. It is mostly performed using external beams of electrons, X-rays, γ-rays from radioactive sources (*e.g.* ^{60}Co), high-energy γ-rays from accelerators, or hadrons (neutrons, protons, heavy ions, etc.). The use of electrons and photons constitutes conventional therapeutic practice, and the data needed are well documented. The rationale of hadron therapy and the associated data needs are treated well in this issue (cf. contributions by Jones, Wambersie, Haight, and Chadwick).

In addition to external radiation therapy, some radioisotopes are used internally to achieve the therapeutic effect. This could involve introducing a radioisotope in a given part of the body (*e.g.* joints, organ, tumour, etc.) either mechanically or via a biochemical pathway. The mechanical introduction takes place through injection of conglomerates or colloids (*e.g.* in joints) or as solids in the form of seeds or stents. This form of therapy is often known as brachytherapy. The use of a biochemical pathway to deliver a therapeutic radioisotope to a specific organ is termed as endoradiotherapy. This type of radiotherapy is a unique cancer treatment modality. It is systemic and non-invasive. The uptake and retention in the tumour can be assessed with a tracer study prior to administering a therapeutic dose. On the other hand, there are also several associated problems, such as, the exact range of the ionising radiation, the *in vivo* stability of the radiotherapeutical, the possibility of immuno chemical changes, etc. Many aspects of endoradiotherapy have been discussed [cf. Refs. 1–11]. In this article, the nuclear data aspect is treated in some detail.

*E-mail: s.m.qaim@fz-juelich.de

2. Criteria for choice of a radionuclide for therapeutic studies

The major criteria for the choice of a radionuclide for endotherapeutic use are suitable decay characteristics and suitable biochemical reactivity. As regards decay properties, the desired half-life is between 6 h and 7 d and the emitted corpuscular radiation should have a suitable linear energy transfer (LET) value and range in the tissue. The ratio of non-penetrating to penetrating radiation should be high. The daughter should be short-lived or stable. As regards biochemical reactivity, the situation is similar to that for diagnostic radiopharmaceuticals. However, the stability of the therapeutical is demanded over a much longer period than that in the case of a diagnostic pharmaceutical. The basis for successful endoradiotherapy thus incorporates

(i) Good and selective concentration and prolonged retention of the radiotherapeutical in the tumour, and
(ii) Minimum uptake in normal tissue.

As a result of the above mentioned criteria, the choice falls on about 30 radionuclides. Most of them are β^--emitters but several of them are α- and Auger electron emitters. In recent years a few β^+-emitters have also found some limited therapeutic application.

3. Radioactive decay data

The half-life (i.e. the physical half-life) of a radioisotope is important. However, in endoradiotherapy of greater importance is the biological half-life, which determines the retention of the radiotherapeutical in the organ. The physical half-life is generally well known; the biological half-life needs to be determined for each individual system via tracer experiments.

The ranges of various types of emitted corpuscular radiation in the tissue are shown in Fig. 1 [cf. 8,11]. The Auger electrons have a range of about 10 μm and can have a therapy effect only if they reach the cell nucleus, *e.g.* by bringing the radioactive source atom to the DNA. The α-particles, on the other hand, have a range of about 100 μm and can have a therapy effect already if they reach the cell membrane, *e.g.* by attachment of the α-emitter to a receptor ligand. The β^--particles have ranges of about 1 mm and more, depending upon their energies. They can lead to therapy effects even if they reach the cell environment. Evidently, achieving the therapy effect with Auger electrons and α-particles

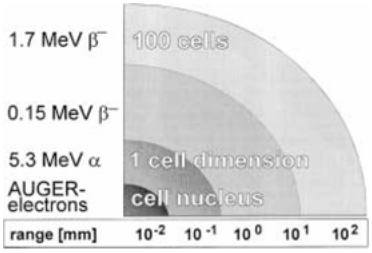

Fig. 1. Correlation between type and energy of corpuscular radiation and the range in tissue (adapted from Refs. [8, 11]).

involves a very subtle approach and demands great skills in biochemistry, radiopharmacology and radiotherapeutical production and application. In the case of β^--particles, the therapeutic applications have been more straightforward, though not very specific.

The methods of internal dose calculation have received extensive attention and well-known computer codes, known as MIRD codes, are now available. As regards diagnostic radionuclides, calculations are done to keep the radiation dose as low as possible. In the case of therapeutic radionuclides, on the other hand, the dose has to be high enough to achieve the therapeutic effect.

In endoradiotherapy, the radioactive decay data thus play a very important role (see also [4, 8]). In particular, a knowledge of the energy and intensity of the ionising radiation is crucial. The effect of low-energy but high intensity electrons, emitted following EC and IT, is not negligible. For widely used therapeutic radioisotopes therefore all sources of secondary electrons must be taken into account. The accuracy in dosimetry depends on the accuracy of the available decay and biochemical data. In general, the available decay database is extensive [cf. 12,13]. The Auger electron spectra, on the other hand, are often not accurately known.

4. Production data

The criteria for the production of therapeutic radioisotopes are generally the same as those for diagnostic radioisotopes, i.e. high radionuclidic purity, high radiochemical purity and high specific radioactivity (cf. contribution by Qaim, this issue). The three types of therapeutic radionuclides, viz. β^--emitters, α-emitters and Auger electron emitters, are treated below separately.

4.1 β^--emitters

The number of β^--emitters of therapeutic relevance is relatively large. The commonly used radionuclides are listed in Table 1. In each case the main decay and production data are outlined. To date, ^{131}I has been most extensively utilized, but in recent years many of the other isotopes listed in Table 1 have been finding enhanced application.

Besides the commonly used β^--emitters, several other β^-- and β^+-emitters have found isolated therapeutic applications. A few examples of β^--emitters are: ^{47}Ca ($T_{1/2}$ = 4.5 d), ^{47}Sc ($T_{1/2}$ = 3.4 d), ^{77}As ($T_{1/2}$ = 1.6 d), ^{105}Rh ($T_{1/2}$ = 1.5 d), ^{159}Gd ($T_{1/2}$ = 18.5 h), ^{161}Tb ($T_{1/2}$ = 6.9 d), ^{165}Dy ($T_{1/2}$ = 2.4 h), ^{166}Dy ($T_{1/2}$ = 3.4 d), ^{169}Er ($T_{1/2}$ = 9.4 d), ^{171}Er ($T_{1/2}$ = 7.5 h), ^{199}Au($T_{1/2}$ = 3.1 d), etc. Some of the β^+-emitters occasionally used in endoradiotherapy are: ^{48}V ($T_{1/2}$ = 16.9 d), ^{52}Mn ($T_{1/2}$ = 5.6 d), ^{124}I ($T_{1/2}$ = 4.2 d), etc. The therapeutic applications of ^{124}I are increasing.

Most of the β^--emitters are produced in a nuclear reactor, and data are needed on neutron capture, sequential neutron capture, (n, z) processes and fission yields. Some special radionuclides like ^{67}Cu and ^{186}Re are produced using both a reactor and an accelerator.

In a nuclear reactor, the (n, γ) process is commonly utilized for production purposes. The excitation function of a typical (n, γ) reaction is shown in Fig. 2 [cf. 14]. The major interest is in the low energy region. The specific radioactivity achieved is rather low. In general, it is limited by the cross section of the (n, γ) reaction, the isotopic abundance of the target isotope and the neutron flux in the reactor. With a view to enhancing the specific radioactivity, either the β^--decay daughter of an (n, γ)-product is used, *e.g.* ^{110}Pd(n, γ) ^{111m,g}Pd $\rightarrow$ ^{111}Ag, or a generator system is developed, *e.g.* ^{90}Sr $\rightarrow$ ^{90}Y and ^{188}W $\rightarrow$ ^{188}Re. Occasionally an alternative route of production is looked for. This may involve the use of an (n, p) reaction in a fast neutron field or the utilization of a cyclotron. The two aspects are considered individually below.

The (n, p) reaction is occasionally utilized to produce therapeutic radionuclides in the medium and heavy mass regions, besides its use in the light mass region. Two demonstrated examples are ^{67}Zn$(n, p)^{67}$Cu and ^{89}Y$(n, p)^{89}$Sr. The product yield in a fission neutron spectrum is low, since the threshold of the (n, p) reaction is rather high, *i.e.* between 2 and 6 MeV. The excitation functions of the ^{67}Zn$(n, p)^{67}$Cu and ^{89}Y$(n, p)^{89}$Sr reactions, measured radiochemically [15, 16], are shown in Fig. 3. If an intense fast neutron field is used, the cross section averaged over the whole spectrum is much higher than for a fission spectrum. A suitable example is the breakup neutron field, produced by 14–15 MeV deuterons on beryllium [cf. 17]. Since presently available high-intensity commercial machines are capable of providing such fast neutron fields, the production of ^{67}Cu and ^{89}Sr via the respective (n, p) reaction appears very advantageous. Another possibility is the use of a spallation

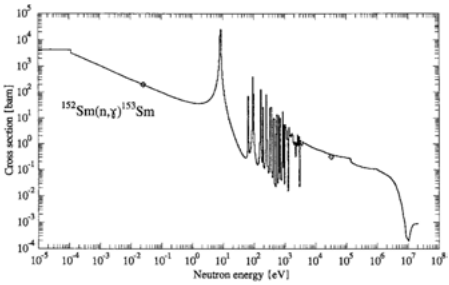

Fig. 2. Excitation function of the ^{152}Sm$(n, \gamma)^{153}$Sm reaction. The data were normalized relative to the very precise measurements at the thermal neutron energy (0.025 eV) and at 30 keV (taken from [14]).

Table 1. Nuclear data relevant to some commonly used therapeutic radionuclides.

Radio-nuclide	$T_{1/2}$	E_{max} of emitted particle in MeV	E_γ in keV (I_γ in %)	Production route	Cross section in mb or remarks[a,b]
			β^--emitters		
^{32}P	14.3 d	1.7 (β^-)		^{31}P(n, γ)	160
				^{32}S(n, p)	70
^{67}Cu	2.6 d	0.6 (β^-)	185 (45)	^{67}Zn(n, p)	1.07
				RbBr(p, spall)	1.6 at 800 MeV
				^{68}Zn(p, $2p$)	10.0 at 71 MeV
^{89}Sr	50.5 d	1.5 (β^-)		^{88}Sr(n, γ)	5.8
				^{89}Y(n, p)	0.31
^{90}Y	2.7 d	2.3 (β^-)		^{89}Y(n, γ)	1250
				^{235}U(n, f)^{90}Sr	Y_{cum}: 5.89%
				^{90}Sr → ^{90}Y generator (28.6 a)	
^{111}Ag	7.5 d	1.0 (β^-)	342 (6)	^{110}Pd(n, γ)^{111m,g}Pd → ^{111}Ag (5.5 h, 23.4 min)	733
^{131}I	8.0 d	0.6 (β^-)	364 (81)	^{130}Te(n, γ)^{131m,g}Te → ^{131}I (25 min, 1.3 d)	230
				^{235}U(n, f)^{131}I	$Y_{cum} = 2.84\%$
^{153}Sm	1.9 d	0.8 (β^-)	103 (28.3)	^{152}Sm(n, γ)	206×10^3
^{166}Ho	1.1 d	1.8 (β^-)	81 (6.2)	^{165}Ho(n, γ)	61×10^3
				^{164}Dy(n, γ)^{165}Dy(n, γ)^{166}Dy (2.4 h)	(2.7; 3.5) × 10^6
				^{166}Dy → ^{166}Ho generator (3.4 d)	
^{177}Lu	6.7 d	0.5 (β^-)	208 (11)	^{176}Lu(n, γ)	1780×10^3
^{186}Re	3.8 d	1.1 (β^-)	137 (8.5)	^{185}Re(n, γ)	114×10^3
				^{186}W(p, n)	100 at 10 MeV[c]
				^{186}W(d, $2n$)	430 at 13 MeV[c]
^{188}Re	17.0 h	2.0 (β^-)	155 (14.9)	^{186}W(n, γ)^{187}W(n, γ)^{188}W (23.7 h)	(36; 70) × 10^3
				^{188}W → ^{188}Re generator (69.0 d)	
			α-emitters		
^{211}At	7.2 h	5.9 (α)		^{209}Bi(α, $2n$)	825 at 28 MeV[c]
(^{211}Po)	(0.52 s)	7.5 (α)			
^{213}Bi	46 min	5.9 (α)	440 (16.5)	Gen. ^{225}Ac (10.0 d) (see below)	radioactive waste
		1.4 (β^-)			
(^{213}Po)	(4.2 µs)	8.3 (α)			
^{225}Ac	10.0 d	5.8 (α)	100 (1.7)	^{229}Th $\xrightarrow{\alpha}$ ^{225}Ra (7880 a)	radioactive waste
				^{225}Ra $\xrightarrow{\beta^-}$ ^{225}Ac (14.8 d)	
				^{226}Ra(p, $2n$) (1600 a)	unknown
			X-ray and Auger electron emitters		
^{67}Ga	3.3 d	Auger electrons	93 (37)	^{67}Zn(p, n)	640 at 11 MeV[c]
				^{68}Zn(p, $2n$)	727 at 20 MeV[c]
^{103}Pd	17.0 d	Auger electrons		^{103}Rh(p, n)	600 at 10 MeV[c]
				^{nat}Ag(p, x)	40 at 28 MeV[c]
^{111}In	2.8 d	Auger electrons	245 (94)	^{111}Cd(p, n)	791 at 12 MeV[c]
				^{112}Cd(p, $2n$)	1025 at 19 MeV[c]
^{125}I	60.1 d	Auger electrons	35 (6.7)	^{124}Xe(n, γ)^{125}Xe → ^{125}I (16.9 h)	165×10^3

a: Neutron capture data are for thermal neutrons and the (n, p) cross sections are fission neutron spectrum averaged values. The fission yields are cumulative yields (Y_{cum}).
b: For charged particle induced reactions the cross section at a suitable energy is given.
c: For this reaction the full excitation function has been measured.

neutron source, generated by high energy protons on a heavy target. In the spectrum, there is a sufficiently strong fast neutron component (with $E_n \geq 10$ MeV), which is ideally suited for (n, p) reactions. Besides ^{67}Cu and ^{89}Sr, several other therapeutic radioisotopes like ^{47}Sc, ^{77}As, ^{105}Rh, ^{153}Sm, ^{159}Gd, ^{166}Ho, ^{177}Lu, ^{188}Re, etc. could also be produced in fast neutron fields via (n, p) reactions on enriched target isotopes.

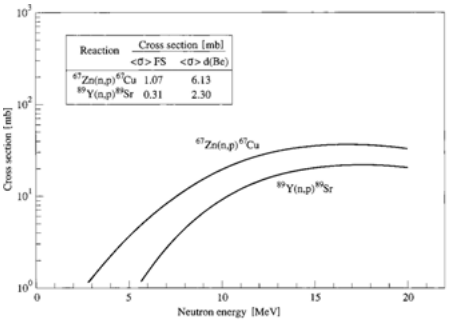

Fig. 3. Excitation functions of $^{67}Zn(n, p)^{67}Cu$ and $^{89}Y(n, p)^{89}Sr$ reactions (adapted from Refs. [15, 16]). From the given curves the average cross sections $\langle\sigma\rangle$ for 14 MeV d(Be) breakup neutron spectrum were deduced. Those values as well as the values for a fission spectrum (FS) are given in the insert. The $\langle\sigma\rangle$ values for the d(Be) breakup neutron spectrum are by a factor of about 6 higher than those for FS.

In recent years attempts have been underway to utilize small and medium-sized cyclotrons to produce some known β^--emitting therapeutic radionuclides via alternative routes as well as to develop other radionuclides of potential therapeutic interest. Two important examples are furnished by ^{67}Cu and ^{186}Re. ^{67}Cu is almost an ideal therapeutic radionuclide. It is produced via an (n, p) reaction in a nuclear reactor (see above), via the spallation of RbBr or via the $^{68}Zn(p, 2p)$ reaction at a high energy accelerator [cf. 18,19]. A recent study showed [20] that the $^{70}Zn(p, \alpha)^{67}Cu$ reaction over the proton energy range $E_p = 18 \rightarrow 12$ MeV, using highly enriched ^{70}Zn as target material, can be used to produce ^{67}Cu at a small cyclotron. The radionuclide ^{186}Re is produced generally via the $^{185}Re(n, \gamma)$-reaction. Since it forms very stable co-ordination compounds (similar to technetium), it has a great therapeutic potential. The main limitation is its specific radioactivity. Two alternative routes making use of the $^{186}W(p, n)^{186}Re$ and $^{186}W(d, 2n)^{186}Re$ reactions are therefore attracting great interest. The excitation functions have been measured [cf. 21–23] and the yields are known (cf. Fig. 4). The yield of ^{186}Re via the $(d, 2n)$ reaction at 15 MeV is much higher than via the (p, n) reaction at 19 MeV [cf. 22].

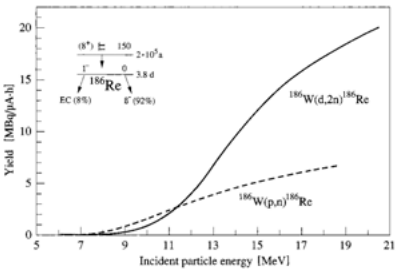

Fig. 4. Calculated integral yields of ^{186}Re ($T_{1/2} = 3.8$ d) formed via proton and deuteron induced reactions on ^{186}W. The relatively low yields of ^{186}Re suggest that the very long-lived high-spin isomer is produced in relatively high yields (adapted from [22]).

Despite the above mentioned four production approaches to increase the specific activity of a β^--emitter (viz. use of a β^--decay daughter of an (n, γ)-product, development of a generator system, application of an (n, p) reaction or use of a cyclotron), there are a large number of cases where there is no alternative to an (n, γ) reaction. Most of those cases refer to rare-earth isotopes which, in recent years, have been attracting enhanced attention [cf. 24] due to their affinity for bone matrix. Fortunately, the (n, γ) cross sections in that mass region are quite high, so that the specific radioactivity achieved is not as low as in many other cases. If an enriched target isotope and a higher flux reactor are used, the achievable specific radioactivity may still be enhanced.

4.2 α-emitters

The commonly used α-emitting radionuclides are listed in Table 1. ^{211}At is important and is produced via the $(\alpha, 2n)$ reaction on bismuth and the data are well known [cf. 25]. ^{225}Ac is a promising radioisotope, both in itself and as a generator for ^{213}Bi. It is obtained as a decay product of ^{229}Th, occurring in the nuclear waste. An interesting production route is the reaction $^{226}Ra(p, 2n)^{225}Ac$ [cf. 26]. Its cross section has hitherto not been measured and constitutes a very challenging task. A few other potentially useful α-emitters are ^{149}Tb ($T_{1/2} = 4.1$ h), ^{212}Bi ($T_{1/2} = 1.0$ h), ^{223}Ra ($T_{1/2} = 11.4$ d), ^{224}Ra ($T_{1/2} = 3.7$ d), etc.

The use of α-emitting radionuclides in endoradiotherapy has been under review almost ever since the discovery of radioactivity. In recent years it has gained more impetus. It should, however, be pointed out that the application of α-emitters demands stringent quality control tests. While working with ^{211}At, for example, a very careful check of the irradiation conditions is mandatory. The α-particle energy to induce the $^{209}Bi(\alpha, 2n)$-reaction is kept at 28.0 MeV otherwise the $^{209}Bi(\alpha, 3n)^{210}At$ reaction would also occur. Its decay product leads to the α-emitting ^{210}Po ($T_{1/2} = 138.4$ d) and would cause excessive extra radiation dose. The field of radiotherapy with α-particles is expected to develop further. Consequently the need for both accurate decay and production data will increase.

4.3 X-ray and Auger electron emitters

Some of the X-ray and Auger electron emitters which have found therapeutic use are listed in Table 1. Evidently, both reactors and cyclotrons are utilized for production purposes. However, the cyclotrons appear to have a higher potential since both X-ray and Auger electron emitters are generally neutron deficient.

The radioisotopes ^{67}Ga and ^{111}In are known more as diagnostic radionuclides since they emit suitable γ-rays. However, their potential as Auger electron emitting therapeutic radionuclides is being increasingly realized. Of particular interest is ^{125}I since it is almost a pure Auger electron emitter and is conveniently attached to a DNA molecule. The radionuclide ^{103}Pd has gained great significance in recent years. The production data were measured

recently [cf. 27,28] and another study is reaching completion under a Jülich/Debrecen cooperation.

Development work on Auger electron emitters is continuing. The recently studied radionuclide ^{140}Nd ($T_{1/2}$ = 3.4 d) [cf. 29] is a pure Auger electron emitter. Similarly the radionuclides ^{195m}Pt ($T_{1/2}$ = 4.0 d) and ^{193m}Pt ($T_{1/2}$ = 4.3 d) are promising Auger electron emitters. However, the presently used production methods ((n, γ) and $(n, n'\gamma)$ process) give very low yields of the latter two radioisotopes. Since in both cases high spin isomers are involved, the ^{3}He- and α-particle induced reactions may be advantageous. In general, Auger electron therapy has a great potential [cf. 30] but calls upon more fundamental work in all related areas.

The radionuclide ^{117m}Sn ($T_{1/2}$ = 13.6 d) is interesting since here conversion electrons, instead of X-rays and Auger electrons, are effective in palliative therapy. Evidently, all data related to conversion electron emission would be needed for dose calculation. The radionuclide is produced via the $(n, n'\gamma)$-process [cf. 31,32]. An alternative method of production involves the ^{3}He- and α-particle induced reactions on In and Cd [33].

5. Some special considerations in studies relevant to production data

Most of the special considerations in nuclear data studies related to the production of diagnostic radioisotopes (cf. contribution by Qaim, this issue), such as, the search for alternative production routes, the role of increasing incident particle energy, and the check of isomeric impurities, are valid also for the therapeutic radionuclides. Furthermore, cross section measurements relevant to the formation of pure β^--emitters and Auger electron emitters are often very challenging since very clean radiochemical separations and thin source preparation are required. The counting methods may involve low-level β^--counting, X-ray spectrometry or liquid scintillation counting. Thus interdisciplinary techniques are of great significance in these studies.

5.1 Analogue positron emitters: therapy planning

A relatively new development in endoradiotherapy with β^--emitters, initiated at Jülich [cf. 34,35], pertains to internal dosimetry through the use of a β^+-emitting analogue of the therapy radionuclide. A quantitative tracer study via PET, prior to therapeutic application, enables therapy planning and an accurate calculation of the dose distribution during the therapy; such calculations had hitherto been done only empirically. A few analogue β^+-emitters of β^--emitting therapy radionuclides are: ^{64}Cu for ^{67}Cu, ^{83}Sr for ^{89}Sr, ^{86}Y for ^{90}Y, ^{124}I for ^{131}I, etc. Evidently, the production and application of those non-conventional β^+-emitters calls upon considerable nuclear data and other development work.

6. Status of nuclear data and conclusions

As discussed above, most of the radionuclides commonly used in endoradiotherapy are β^--emitters. They are mainly produced in a nuclear reactor and the status of nuclear data is generally good [cf. 36–39]. However, to date no evaluated data file in this respect has been developed. Regarding the β^-- and β^+-emitters which have hitherto found only limited application, or which are of potential interest, the cross section data base varies from case to case. For reactor-produced radionuclides it is good; for cyclotron produced radioisotopes, however, more work may be needed. In particular, an evaluation of the existing data is required. The available information on the established α-emitter ^{211}At is good. Similarly the decay and production data of the commonly used Auger electron emitters are well known. For potentially useful α-emitters and Auger electron emitters, however, the available information both on decay and production data is often not detailed enough. Since endoradiotherapy is a fast developing field, and new radionuclides emitting the latter two types of corpuscular radiation are being constantly suggested, the need for nuclear data is enhancing. Considerable amount of experimental, theoretical and evaluation work would be necessary to meet those needs. The experimental work is often very challenging since a quantitative measurement of the radioactivity via X-ray spectrometry or Auger electron counting is needed. Theory and evaluations face difficulties since isomeric states with highly converted isomeric transitions are involved. In the latter case, a detailed information on the conversion coefficients is also needed. In short, a concerted effort is called for to build a reliable database relevant to production and application of therapeutic radionuclides.

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Appendix V

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Development of novel positron emitters for medical applications: nuclear and radiochemical aspects

By S. M. Qaim*

Institut für Neurowissenschaften und Medizin, INM-5: Nuklearchemie, Forschungszentrum Jülich GmbH, 52425 Jülich, Germany

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Novel positron emitter / Nuclear data / Low and intermediate energy reactions / Targetry / Radiochemical separation / Production yield / Quality control / Radionuclide generator / New generation high power accelerator

Summary. In molecular imaging, the importance of novel longer lived positron emitters, also termed as non-standard or innovative PET radionuclides, has been constantly increasing, especially because they allow studies on slow metabolic processes and in some cases furnish the possibility of quantification of radiation dose in internal radiotherapy. Considerable efforts have been invested worldwide and about 25 positron emitters have been developed. Those efforts relate to interdisciplinary studies dealing with basic nuclear data, high current charged particle irradiation, efficient radiochemical separation and quality control of the desired radionuclide, and recovery of the enriched target material for reuse. In this review all those aspects are briefly discussed, with particular reference to three radionuclides, namely ^{64}Cu, ^{124}I and ^{86}Y, which are presently in great demand. For each radionuclide several nuclear routes were investigated but the (p, n) reaction on an enriched target isotope was found to be the best for use at a small-sized cyclotron. Some other positron emitting radionuclides, such as ^{55}Co, ^{76}Br, ^{89}Zr, ^{82m}Rb, ^{94m}Tc, ^{120}I, *etc.*, were also produced *via* the low-energy (p, n), (p, α) or (d, n) reaction. On the other hand, the production of radionuclides ^{52}Fe, ^{73}Se, ^{83}Sr, *etc.* using intermediate energy (p, xn) or (d, xn) reactions needs special consideration, the nuclear data and chemical processing methods being of key importance. In a few special cases, a high intensity ^{3}He- or α-particle beam could be an added advantage. The production of some potentially interesting positron emitters *via* generator systems, for example ^{44}Ti/^{44}Sc, ^{72}Se/^{72}As and ^{140}Nd/^{140}Pr is considered. The significance of new generation high power accelerators is briefly discussed.

1. Introduction

Radionuclides find application in many fields. However, their major use is in medicine, both for diagnosis and therapy [*cf.* 1]. This is manifested by the International Symposium on Radiopharmaceutical Sciences, held biennially in some part of the world. The underlying principle of an *in vivo* diagnostic application is that the radiation dose to the patient is as low as possible, compatible with the desired quality of imaging. This calls upon the use of very special radionuclides which can be detected efficiently from outside of the body. In general, short-lived γ-ray emitters or positron emitters are commonly used, the former finding application in Single Photon Emission Computed Tomography (SPECT) and the latter in Positron Emission Tomography (PET). In contrast, an internal therapeutic application requires that a certain amount of dose is specifically deposited in a malignant tissue. Thus for internal radiotherapy, radionuclides emitting corpuscular radiation (α- or β^- particles, conversion and/or Auger electrons) are of interest.

The production of radionuclides for medical applications is carried out using both nuclear reactors and cyclotrons. The most commonly used SPECT radionuclide ^{99m}Tc ($T_{1/2} = 6.0$ h) is produced using a nuclear reactor. Its widespread use is mainly based on its convenient availability as a ^{99}Mo/^{99m}Tc generator. Many of the cyclotron produced γ-ray emitting radionuclides, such as ^{67}Ga ($T_{1/2} = 78.3$ h), ^{111}In ($T_{1/2} = 2.9$ d), ^{123}I ($T_{1/2} = 13.2$ h) and ^{201}Tl ($T_{1/2} = 73.1$ h) also find application. They are commercially available. In recent years, however, the positron emitting radionuclides have been gaining more significance because PET has made it possible to quantitatively measure regional activities of a molecule (labelled with a positron emitter) with high sensitivity and a spatial resolution of a few mm. The commonly used short-lived organic positron emitters, *viz.* ^{11}C ($T_{1/2} = 20.3$ min), ^{13}N ($T_{1/2} = 10.0$ min), ^{15}O ($T_{1/2} = 2.0$ min) and ^{18}F ($T_{1/2} = 110$ min), are produced *via* low-energy nuclear reactions at small-sized cyclotrons [*cf.* 2]. Besides those four organic positron emitters, two other short-lived positron emitters, namely ^{68}Ga ($T_{1/2} = 67.6$ min) and ^{82}Rb ($T_{1/2} = 1.3$ min), are produced *via* generator systems. Their respective long-lived parents ^{68}Ge ($T_{1/2} = 271$ d) and ^{82}Sr ($T_{1/2} = 25.3$ d) are produced through intermediate energy nuclear reactions. The whole PET technology (consisting of cyclotron, radionuclide production unit, and automated radiosynthesis apparatus) is now commercially available.

Among the therapeutic radionuclides, ^{131}I ($T_{1/2} = 8.02$ d) is by far the most important, having an established place in the management of follicular thyroid carcinoma. The other radioiodine, ^{125}I ($T_{1/2} = 59.41$ d), is used in Auger electron therapy. Several other reactor produced radionuclides,

*E-mail: s.m.qaim@fz-juelich.de.

for example ^{32}P ($T_{1/2} = 14.3$ d), ^{89}Sr ($T_{1/2} = 50.5$ d), ^{90}Y ($T_{1/2} = 2.7$ d) and ^{153}Sm ($T_{1/2} = 1.9$ d), find application in palliative treatment. In recent years cyclotrons have also been increasingly used to produce some therapeutic radionuclides, in particular those emitting low energy but highly ionising radiation [*cf*. 3].

Today, research work on radionuclides for nuclear medicine is carried out mainly in two directions:

1. Development of novel longer lived positron emitters.
2. Development of novel low-energy but highly ionising radiation emitters for internal radiotherapy.

This article deals with nuclear and radiochemical aspects of development of novel positron emitters. Those radionuclides can only be produced at cyclotrons (or accelerators). With the increasing significance of PET in diagnostic nuclear medicine, the need for longer lived novel positron emitters, also termed as non-standard or innovative positron emitters, has been increasing, especially for studying slow metabolic processes [*cf*. 4]. Some aspects of their production have been considered [*cf*. 5–8]. The present review discusses their production methodologies in more detail.

2. Fundamental considerations in development of novel positron emitters

The development of a novel positron emitter has to comply with certain constraints with respect to production possibilities (*e.g.* type of available cyclotron, yield of nuclear reaction to be used, enrichment of the target material, *etc.*). It calls upon interdisciplinary work comprising nuclear data measurement, high-current targetry, chemical processing, automation of the procedure and quality control of the product. Furthermore, its suitability for imaging, which is related to its decay characteristics, also needs to be demonstrated. A discussion of all those aspects, is given below, furnishing examples from a few recent investigations.

2.1 Nuclear data

2.1.1 Reaction cross section data

In cyclotron production of radionuclides, the reaction cross section data play a very important role [*cf*. 9, 10]. One needs the full excitation function of the nuclear process under consideration to be able to calculate the expected production yield with a reasonable accuracy. The data are needed mainly for the optimization of the production route, *i.e.* to maximize the yield of the desired product and to minimize the yields of the radioactive impurities. The calculated yield value of the desired product represents the maximum yield which can be expected from a given nuclear process. It should be pointed out that, whereas the non-isotopic impurities produced can be removed by chemical separations, the level of isotopic impurities can be suppressed only by using an enriched isotope as target material and/or by a careful selection of the particle energy range effective in the target, the latter information being derived from the respective excitation function.

Besides isotopic impurities, isomeric impurities also need to be considered. Several novel medical radionuclides have isomeric states, which are rather disturbing. A few

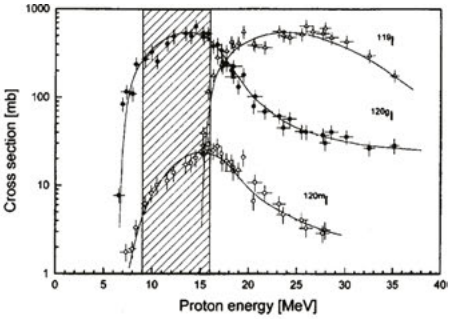

Fig. 1. Excitation functions of $^{120}Te(p, xn)$-reactions leading to the formation of ^{120m}I, ^{120g}I and ^{119}I. The solid lines are eye-guides. The shaded area gives the optimum energy range for the production of ^{120g}I (after Ref. [13]).

examples are $^{86m}Y(^{86g}Y)$, $^{94m}Tc(^{94g}Tc)$ and $^{120g}I(^{120m}I)$. The isomeric impurities cannot be controlled through a careful adjustment of the energy window (as mentioned above). Since the isomeric cross section ratio is primarily dependent on the type of reaction involved [*cf*. 11], it is essential to investigate all the possible production routes and then to choose the reaction and the energy range giving the best results. Obviously, nuclear data play here a very important role. Nuclear reaction cross section measurements performed [12, 13] in connection with the development of the positron emitter ^{120g}I ($T_{1/2} = 1.35$ h) provide a good example of the importance of nuclear data. The results on the $^{120}Te(p, xn)^{119,120m,g}I$ reactions [13] are shown in Fig. 1. The energy range $E_p = 16 \rightarrow 9$ MeV appears to be optimum for the production of ^{120g}I. Over this energy range the calculated thick target yield of ^{120g}I is high (2.3 GBq/μA h), and the levels of the impurities are: ^{120m}I (4.8%) and ^{119}I (4.4%). The impurity ^{119}I is not a problem. Being short-lived ($T_{1/2} = 19.1$ min), it almost completely decays out during the separation of ^{120g}I from the irradiated target. The isomeric impurity ^{120m}I ($T_{1/2} = 53$ min) is also shorter lived as compared to ^{120g}I; its relative contribution would therefore decrease with the decay time. On the other hand, if the reaction $^{122}Te(p, 3n)^{120m,g}I$ is used [12] for the production of ^{120g}I, with a calculated thick target yield of ^{120g}I of 3.6 GBq/μA h over the energy range of $E_p = 37 \rightarrow 32$ MeV, the contribution of ^{120m}I may amount up to 25%.

Extensive nuclear data studies in connection with the development of innovative positron emitters have been carried out at the Forschungszentrum Jülich over the last 25 years. In most of the cases the low-energy (p, n) reaction on a highly enriched target isotope was found to be ideal. The pertinent examples are: $^{64}Ni(p, n)^{64}Cu$ [14], $^{76}Se(p, n)^{76}Br$ [15], $^{82}Kr(p, n)^{82m}Rb$ [16], $^{86}Sr(p, n)^{86}Y$ [17], $^{94}Mo(p, n)^{94m}Tc$ [18], $^{120}Te(p, n)^{120g}I$ [13] and $^{124}Te(p, n)^{124}I$ [19]. In the case of ^{64}Cu, ^{86}Y and ^{124}I, the three most prominent novel positron emitters, the suggested (p, n) reaction has become the method of choice for obtaining a high-purity product.

Besides the (p, n) reaction, for several radionuclides other low and intermediate energy reactions, for example,

(p,α), (d,n), (p,xn), (d,xn), $(^3\mathrm{He},xn)$ and (α,xn), have also been investigated. Furthermore, in several cases, for example ^{64}Cu and ^{124}I, extensive comparisons of various production routes have been presented [*cf*. 8, 20]. Detailed evaluations of the data using nuclear model calculations and statistical fitting procedures have also been performed for several radionuclides [*cf*. 21–24]. Thus the nuclear reaction cross section database for the production of innovative positron emitters appears to have considerably improved in recent years.

2.1.2 Decay data

In addition to the production data, some attention also needs to be paid to the radioactive decay data. Those data are of considerable significance in determining the quality of the image and the radiation dose deposited while using that radionuclide. In general, the decay data are fairly well known (cf. *e.g.* Evaluated Nuclear Structure and Decay Data File (ENSDF)). A problem with many of the novel positron emitters, however, is that the positron emission intensity is often rather low and not exactly known (*cf*. Report: IAEA-INDC(NDS)-0535 (2009)), thereby causing some uncertainty in the quantification of tomographic scans. Since decay schemes of many of the medically interesting radionuclides were determined using mixtures of radionuclides, often utilising detectors with rather poor resolution, it appears worthwhile to reinvestigate some of the special radionuclides in more detail using radiochemical techniques. Many of those medical radionuclides can now be produced with very high purities; the use of ultrapure sources should thus provide accurate information on the decay data as well. Some measurements on the positron emission intensities in the decay of ^{64}Cu, ^{76}Br, ^{120g}I and ^{124}I have recently been carried out [25, 26]. Similar measurements on several other novel positron emitters also need to be performed.

2.2 High current targetry

The high current irradiation technology needed for medium to large scale production of a radionuclide is rather different from the low current irradiations performed for nuclear reaction cross section measurements. In fact the development of targetry for irradiations with intense charged particle beams constitutes one of the major efforts in cyclotron production of radionuclides [*cf*. 27]. The loss of energy of the charged particle in the target generates a lot of heat and, if high currents are used, the power density effective at a target may reach a high value (up to a few kW cm^{-2}). An efficient heat transfer is thus one of the prime requirements in target construction. Several other considerations for target design are: (1) ease of chemical separation of the radioactive product, (2) high yield of the product, (3) radionuclidic purity, (4) chemical reactivity and specific activity of the desired product, and (5) recovery of enriched target material.

Whereas in the production of conventional short-lived organic positron emitters for PET, which are isotopes of light elements, gaseous and liquid targets are used, for the production of innovative positron emitters under consideration here, use is generally made of solid targetry [*cf*. 3, 27], as it is done in the case of several SPECT radionuclides, *e.g.* ^{67}Ga, ^{111}In and ^{201}Tl. Occasionally a gas target is also used.

Irradiation of solid material is often carried out in a conventional target system, where the front side consists of a double foil window through which He gas flows for cooling the target material. The back side of the target is cooled by flowing water. The beam impinges on the target orthogonally. Rather commonly employed solid targetry today involves preparation of a relatively thick layer (up to a few hundred μm) of the target material *via* electrolytic deposition on a metal backing, and irradiations are performed with slanting beams. In other cases, where no elemental material is employed, suitably prepared alloys or intermetallic compounds are also used. Occasionally, the target material is an oxide which is spread on another metal, melted or sintered, and then used as an irradiation target.

A typical solid target system used, *e.g.* for the production of ^{55}Co and ^{64}Cu *via* the reactions ^{58}Ni$(p,\alpha)^{55}$Co and ^{64}Ni$(p,n)^{64}$Cu, respectively, is shown in Fig. 2 [28]. The corresponding highly enriched nickel isotope is electroplated on an oval shaped gold backing which fits in a target holder designed to be exposed to the charged particle beam at an angle of 20°. The target holder is cooled at the back by a water jet. Beam currents of about 30 μA are commonly used. With a better design of the system, beam currents of up to 300 μA could be put on the target. The same target set up has also been employed in the production of ^{124}I *via* the ^{124}Te(p,n)-reaction. In this case the target material $^{124}TeO_2$ is melted on a Pt backing (rather than electroplating on gold) which is then attached to the target holder for irradiation.

For noble gases as target material, *e.g.* for the production of ^{38}K, ^{81}Rb, ^{82m}Rb and ^{83}Sr *via* the reactions ^{38}Ar$(p,n)^{38}$K, ^{82}Kr$(p,2n)^{81}$Rb, ^{82}Kr$(p,n)^{82m}$Rb and ^{82}Kr$(^3\mathrm{He},2n)^{83}$Sr, respectively, a typical target system used is shown in Fig. 3 [29]. The conical shaped target has a double foil window in front, which is cooled by He gas. The other accessories form a complex system for safe handling of the highly enriched rare noble gas (filling the target, irradiation and its recovery for reuse). Beam currents of about 30 μA are used.

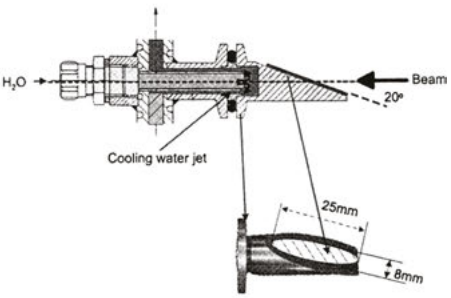

Fig. 2. Typical solid target system used for the production of ^{55}Co, ^{64}Cu or ^{124}I *via* the nuclear reactions ^{58}Ni$(p,\alpha)^{55}$Co, ^{64}Ni$(p,n)^{64}$Cu and ^{124}Te$(p,n)^{124}$I, respectively. In the first two cases, the highly enriched target material is electrolytically deposited on oval shaped gold backing; in the latter case $^{124}TeO_2$ is melted on a Pt backing. The target fits in a target holder which is exposed to the proton beam at an angle of 20° and is cooled at the back by a water jet (after Ref. [28]).

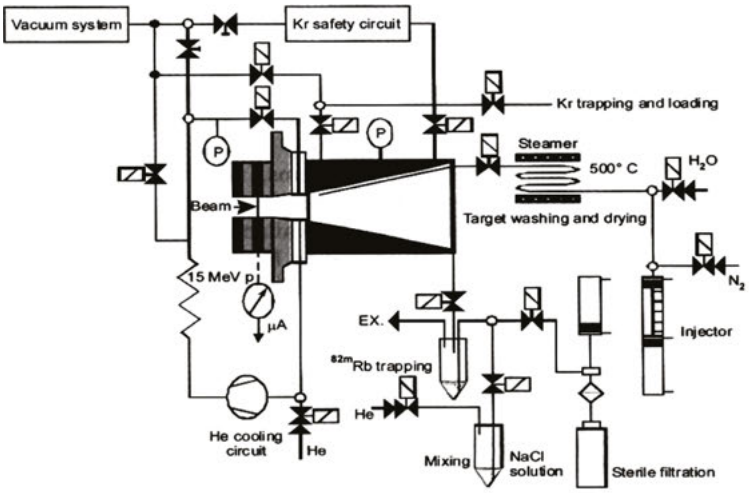

Fig. 3. Typical gas target system used for the production of ^{82m}Rb *via* the nuclear reaction ^{82}Kr$(p, n)^{82m}$Rb. The conical shaped target has a double foil window in front, which is cooled by He gas. The other accessories form a compact system for safe handling of the highly enriched rare gas. The product ^{82m}Rb is efficiently removed from the target inner wall by introducing steam, and is collected in water. The same system has been used also for the production of ^{38}K, ^{81}Rb or ^{83}Sr *via* the nuclear reactions ^{38}Ar$(p, n)^{38}$K, ^{82}Kr$(p, 2n)^{81}$Rb and ^{82}Kr$(^3$He, $2n)^{83}$Sr, respectively; in each case proper target gas and charged particle beam energy have to be used (adapted from Ref. [29]).

After irradiation, at first the enriched target gas is recovered. The product alkali or alkaline earth metal activity remains adsorbed on the inner walls of the target. For its removal, superheated steam (at 500 °C) is introduced in the target. On cooling, the condensed water is forced out by a stream of nitrogen and is efficiently collected in a trap. The process is repeated seven times so that > 90% of the activity is accumulated in about 2.5 mL of water.

2.3 Chemical processing

There are two major aims of chemical processing:

1. to isolate the desired radionuclide in pure form,
2. to recover the enriched material for reuse.

In production of novel positron emitters, both dry and wet chemical separation methods have been applied [*cf*. 3]. The dry method involves distillation and thermochromatography. The best example of the dry distillation technique is furnished by separation of the increasingly important radioiodines, especially ^{120g}I and ^{124}I, from irradiated $^{120}TeO_2$ and $^{124}TeO_2$ targets, respectively, at 755 °C [*cf*. 30]. Radioiodine is collected almost quantitatively and the target is regenerated (without much loss) for the next production run. Thermochromatography, on the other hand, involves the formation of a chemical species of the radioactive product which leads to its removal from the irradiated target but the vapour pressure of which is not high enough to allow its transport to large distances. The activity gets deposited in the cooler part of the thermochromatographic tube from where it is generally removed by rinsing. The method has been successfully employed in the separation of ^{73}Se [31, 32], ^{75}Br [33], ^{76}Br [34] and ^{94m}Tc [35]. The thermochromatographic behaviour of a proton-irradiated Cu_3As-target in an oxygen atmosphere is shown in Fig. 4 [32]. The major radioactive products formed are ^{73}Se, ^{74}As and ^{65}Zn through the nuclear reactions ^{75}As$(p, 3n)^{73}$Se, ^{75}As$(p, pn)^{74}$As and ^{65}Cu$(p, n)^{65}$Zn, respectively. The removal of $[^{74}As]As_2O_3$ is carried out at about 660 °C and that of radioselenium at about 1100 °C, while ^{65}Zn remains in the quartz tube within the oven area. It should, however, be mentioned that thermochromatography only serves to concentrate the desired activity at one point. It does not necessarily give a pure product. For a cleaner separation, a subsequent wet chemical step is often necessary. On the other hand, the recovery of the enriched target material is relatively easy while using distillation or thermochromatography for the separation of the desired radioactive product.

In many production processes a wet chemical procedure is absolutely necessary. Preferentialy solvent extraction and ion-exchange techniques are used but occasionally a prior concentration of the radionuclide is achieved through coprecipitation, adsorption, *etc.* Several of the emerging radionuclides are separated using these methods. In the production of ^{64}Cu *via* the ^{64}Ni(p, n)-reaction, for example, anion-exchange chromatography was applied [*cf*. 14]. In the production of ^{86}Y *via* the ^{86}Sr(p, n)-reaction the separation proceeds in two steps [36]. The irradiated enriched $^{86}SrCO_3$ is dissolved in a small volume of conc. HCl and no-carrier-added ^{86}Y is coprecipitated with $La(OH)_3$ by addition of NH_4OH solution. The precipitate is centrifuged off and taken up in a few drops of HCl. The separation of radioyttrium from inactive La is then effected through ion-exchange chromatography by elution with α-hydroxyisobutyric acid,

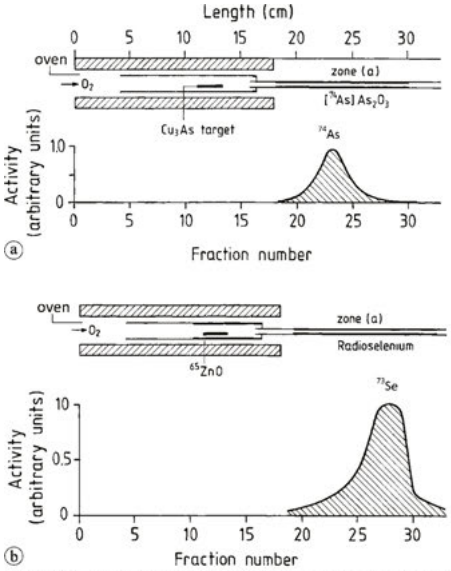

Fig. 4. Two step thermochromatographic procedure for separation of radioselenium from the Cu_3As-target irradiated with protons (adapted from Ref. [32]). (**a**) Removal of [^{74}As]As_2O_3 from the target in an oxygen stream at 660 °C to zone (a). The deposition profile was determined using the 595 keV γ-ray of ^{74}As. (**b**) Replacement of the external quartz tube by another quartz tube. Removal of radioselenium at 900–1100 °C to zone (a). The activity profile was determined using the 361 keV γ-ray of ^{73}Se. The volatalized ^{65}ZnO remains in the quartz tube within the oven area.

either by normal pressure [36] or in combination with high performance liquid chromatography [37]. Fig. 5 shows the elution profile of radioyttrium. The activity amounting to several GBq is collected in only 150 μL solution. The separation of ^{52}Mn, ^{52}Fe, ^{55}Co, ^{89}Zr, *etc.* is also carried out *via* ion-exchange chromatography.

2.4 Remote handling

In a real production run the aim is to achieve the maximum batch yield of the radionuclide (with the minimum level of the radionuclidic impurities). The amount of radioactivity involved is rather high (often up to 100 GBq). All the unit operations, such as removal of the irradiated target from the beamline, its transfer to the radiochemistry laboratory, and finally the chemical processing, need to be handled remotely in order to decrease the radiation dose to the researcher. Some of those operations even demand automated methods to avoid human errors. Many of the novel positron emitters are still at the experimental stage of production for local use. On the other hand, a few of them have passed that stage; their large scale production now appears necessary and useful. The examples are: ^{64}Cu, ^{86}Y and ^{124}I. In those cases the need for development of remotely controlled or even automated methods of production is imminent.

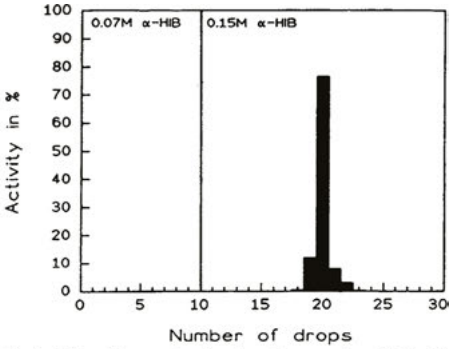

Fig. 5. Elution diagram of radioyttrium from a column filled with Aminex A5 cation-exchanger (4 mm ∅ × 40 mm). The no-carrier-added ^{86}Y, coprecipitated with $La(OH)_3$, was dissolved in a small volume of HCl and transferred to the above column. Elution was done with α-hydroxyisobutyric acid (α-HIB). The ^{86}Y activity was collected in a few drops (after Ref. [36]).

2.5 Quality control of the product

An important step in a chain of operations for the production of a novel radionuclide consists of quality assurance of the obtained product. In general, four characteristics need to be considered. These are radionuclidic purity, radiochemical purity, chemical purity and specific activity. A brief discussion of each item is given below.

The *radionuclidic purity* means the absence of any other radionuclide. This is achieved *via* the choice of a suitable nuclear process and energy range, combined with a clean chemical separation. The radionuclide ^{124}I, for example can be produced *via* a large number of reactions [*cf*. 20]. However, its production is carried out today mainly using the ^{124}Te(p, n)-reaction on a highly enriched $^{124}TeO_2$ target over the energy range of $E_p = 14 \rightarrow 9$ MeV. Although the yield of this process is not very high, the resulting product is very pure (^{125}I impurity < 0.1%).

The *radiochemical purity* means that the radiochemically separated product is in the form of one major chemical species. In the case of a solid target the separated radionuclide is generally brought into a desired radiochemical form through oxidation/reduction cycles. The radiochemical purity is generally tested by radiochromatographic methods, such as thin layer chromatography (TLC), *e.g.* in production of ^{94m}Tc [*cf*. 35], high performance liquid chromatography (HPLC), *e.g.* in production of ^{120g}I and ^{124}I [*cf*. 30], and ion-exchange chromatography, *e.g.* in production of ^{86}Y [*cf*. 36, 37]. A typical example relevant to ^{94m}Tc production [35] is shown in Fig. 6. The thermochromatographically separated fraction was dissolved in a small volume of 10^{-4} M NaOH and the solution subjected to TLC analysis. Two species were detected (Fig. 6a), one representing TcO_4^- ($R_f = 0.95$) and amounting to 80–90%, and the other a radiochemical impurity ($R_f \approx 0$) with the contribution of 5–10%. When the solution was passed through a small alumina column, it was purified; the technetium then occurred almost 100% in the chemical form of pertechnetate (Fig. 6b).

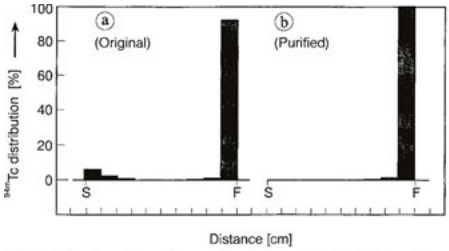

Fig. 6. Radiochemical quality control of the radiotechnetium solution (after dissolution of the thermochromatographically separated technetium fraction from a MoO_3 target) in 10^{-4} M NaOH: **(a)** original solution, **(b)** after final purification using alumina column chromatography. S denotes starting point and F the final position. Thin layer chromatography was done on Merck TLC plates (silica gel 60 F_{254}), and acetone was used as solvent system (after Ref. [35]).

The *chemical purity* means the absence of inactive impurities which are generally introduced *via* the chemical reagents used in the production of the radionuclide. Apart from their possible toxicity, those impurities may form complexes with the radionuclide, thereby decreasing its reactivity. The chemical purity appears to be more important in the case of metal radionuclides, such as novel positron emitters, than for radionuclides used in the labelling of organic compounds. For checking the chemical purity one or more of the standard techniques, such as atomic absorption (AA) spectroscopy, ultraviolet (UV) or infrared (IR) detection, inductively coupled plasma-mass spectrometry (ICP-MS) and polarography are used.

The *specific activity* is defined as the radioactivity per unit mass of the product. Cyclotron production of radionuclides leads inherently to high specific activity products, unless some carrier inadvertently gets introduced by impure target material during the chemical processing stage. The co-production of stable or longer-lived species also needs to be considered since it would decrease the specific activity of the desired product. In case of metal radionuclides it is quite a serious consideration; very pure reagents and clean working methods are absolutely needed. For estimating the specific activity, generally the radioactivity of the whole batch is measured in an ionisation chamber and the mass is determined using a sensitive detection method, such as UV, IR, refractive index or conductivity measurement.

It should be mentioned that the above discussed four quality assurance tests refer to the radionuclide in its original form. They are crucial with respect to further processing of the radionuclide. If the radionuclide is converted into a radiopharmaceutical for human use, several further stringent tests, like those for sterility, apyrogenicity and toxicity, also become mandatory.

2.6 Suitability of novel positron emitters for PET imaging

In contrast to standard positron emitters, PET imaging with novel or non-standard positron emitters is often associated with two major problems:

1. High end-point energy of the positron,
2. Emission of γ-rays accompanying the positron.

These may cause reduction of spatial resolution and blurring of the image. PET phantom measurements are therefore needed to demonstrate the suitability of a novel positron emitter for imaging purposes [*cf*. 38–44]. The high positron end-point energies of ^{66}Ga, ^{76}Br and ^{120g}I (in each case around 4 MeV), for example, limit the use of those radionuclides. Similarly the large number of γ-rays associated with several radionuclides, *e.g.* ^{76}Br and ^{86}Y, cause considerable distortion of images. However, with the development of efficient algorithms these effects can be often efficiently corrected [*cf*. 38–44]. Thus, prior to application, the correction factor needs to be determined individually for each novel positron emitter through PET phantom measurements.

3. Production of novel positron emitters

Several types of accelerators and nuclear reactions have been used for the production of novel radionuclides. A discussion is given below.

3.1 Production using low-energy reactions

Most of the novel positron emitters have been developed at laboratories where standard positron emission tomography facilities already existed. Since at PET centres generally only a small-sized cyclotron is available (with $E < 20$ MeV), almost all of the development work has been carried out using those cyclotrons. A brief overview of the production routes using low-energy reactions is given in Table 1 [*cf*. 13–19, 28–30, 34–37, 45–50, 53–92]. In each case, except for ^{45}Ti, ^{52}Mn, ^{72}As, ^{89}Zr and ^{90}Nb, highly enriched target material was used. The suitable energy range, the thick target yield calculated from the excitation function, the expected radionuclidic impurities and the relevant references are given. For production, in general, solid targetry was used, except for the ^{38}Ar$(p, n)^{38}$K, ^{78}Kr$(p, \alpha)^{75}$Br, ^{78}Kr$(d, \alpha)^{76}$Br and ^{82}Kr$(p, n)^{82m}$Rb reactions where gas targetry was employed. Technical development work has been performed in many institutes around the world but several of the radionuclides have been investigated only in one or two laboratories, with limited application. Radionuclides of more general interest are ^{55}Co, ^{61}Cu, ^{72}As, ^{76}Br, ^{89}Zr, ^{94m}Tc and ^{120g}I. Their production methods have been well worked out [*cf*. 14, 34, 35, 68–70, 81–89] and radionuclidically pure products are available for medical development work. On the other hand, three novel positron emitters, namely ^{64}Cu, ^{86}Y and ^{124}I, have become of wide interest and are now in great demand. Their production is discussed in some detail below.

The radionuclide **^{64}Cu** emits low-energy positrons, has no disturbing γ-ray and has a suitable half-life to study slow metabolic processes. The production route ^{64}Ni$(p, n)^{64}$Cu, originally suggested by the Jülich group [14], has been further developed in several other laboratories [*cf*. 45–50]. In a recent work sophisticated targetry calculations have been done [50]. Batches of about 40 GBq are now routinely produced. Several intermediate energy reactions have also been investigated for the production of ^{64}Cu [for review *cf*. 8, 21], but the levels of impurities are higher.

Table 1. Novel PET radionuclides produced at low-energy cyclotrons ($E < 20$ MeV).

	Decay data[a]				Production data[b]				
Radio-nuclide	$T_{1/2}$	I_{β^+} [%]	E_{β^+} [keV]	E_γ [keV (%)]	Common production route	Energy range [MeV]	Calculated yield [MBq/μA h]	Radionuclidic impurity (%)	Reference
^{38}K	7.6 min	99.4	2724	2168 (99.9)	^{38}Ar(p,n)	16 → 12	777	–	[63]
^{45}Ti	3.08 h	84.8	1040	719 (0.15)	^{45}Sc(p,n)	12.5 → 10.5	337[d]	–	[64,65]
^{51}Mn	46.2 min	97.1	2185	749 (0.26)	^{50}Cr(d,n)	10 → 4	700	^{52m}Mn (< 4)	[66]
^{52}Mn	5.6 d	29.6	576	1434 (100) 935 (94)	^{nat}Cr(p,xn)	20 → 10	0.4	^{54}Mn (< 0.5)	[66,67]
^{55}Co	17.5 h	76.0	1498	931 (75) 477 (20)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 → 7 10 → 5	14 32	^{57}Co (0.5) ^{56,57}Co (< 0.1)	[68] [69,70]
^{61}Cu	3.3 h	61.0	1215	283 (12.5) 656 (10.7)	^{61}Ni(p,n) ^{64}Zn(p,α)	12 → 9 19 → 10	647 366	^{60}Cu (14.6) ^{60}Cu (0.5)	[14] [82]
^{62}Cu	9.7 min	97.4	2926	1173 (0.34)	^{62}Ni(p,n)	14 → 10	13×10^3	^{61,64}Cu (0.8)	[71]
^{64}Cu	12.7 h	17.8	653	1346 (0.53)	^{64}Ni(p,n)	12 → 9	236	^{61}Cu (0.4)	[14,72]
^{66}Ga	9.5 h	56[c]	4153	1039 (38) 2752 (23.8)	^{66}Zn(p,n)	13 → 8	433	–	[73]
^{72}As	26.0 h	87.8	3334	834 (79.5)	^{nat}Ge(p,xn)	18 → 8	93	^{71}As (< 10)	[74]
^{75}Br	1.6 h	73	2008	286 (92)	^{78}Kr(p,α) ^{74}Se(d,n)	17 → 11 12 → 8	70 509	– ^{74m}Br (< 1)	[75] [77]
^{76}Br	16.2 h	58.2	3941	559 (74) 657 (15.9) 1854 (14.7)	^{76}Se(p,n) ^{78}Kr(d,α)	15 → 8 13 → 4	360 0.06	– –	[15] [76]
^{81}Rb	4.6 h	27[c]	1026	190 (64.3) 446 (23.3)	^{80}Kr(d,n)	14 → 6	372	^{82m}Rb(< 0.1)	[78]
^{82m}Rb	6.5 h	21[c]	899	776 (84.5) 1044 (32.1) 1317 (23.7)	^{82}Kr(p,n)	14.5 → 10	370	^{81}Rb (0.01)	[16]
^{86}Y	14.7 h	33[c]	2019	1077 (82.5) 628 (32.6) 1153 (30.5)	^{86}Sr(p,n)	14 → 10	400	^{87m,g}Y (3)	[17]
^{89}Zr	78.4 h	22.3	897	909 (100)	^{89}Y(p,n)	12 → 6	43	^{88}Zr (< 0.1)	[79]
^{90}Nb	14.6 h	51.2	1500	1129 (92.7) 2319 (82.0) 141 (66.7)	^{nat}Zr(p,xn)	15 → 8	423	^{92,95,96}Nb (3)	[80]
^{94m}Tc	52 min	72.0	2470	871 (94.2)	^{94}Mo(p,n)	13 → 7	2×10^3	^{94g}Tc (6)	[18,89]
^{120g}I	1.3 h	56.0	4593	560 (73) 1522 (11.2)	^{120}Te(p,n) ^{120}Te$(d,2n)$	15 → 9 14 → 9	2×10^3 0.9	^{120m}I (4.8) ^{121}I (68)	[13] [88]
^{124}I	4.18 d	22.0	2137	603 (61) 1691 (10.4) 723 (10.0)	^{124}Te(p,n) ^{124}Te$(d,2n)$	12 → 8 14 → 10	16 17.5	^{125}I (0.1) ^{125}I (1.7)	[19] [54]

a: Decay data were mostly taken from ENSDF. For ^{64}Cu, ^{76}Br, ^{120g}I and ^{124}I the I_{β^+} values were adopted from Refs. [25,26].
b: Using highly enriched isotope as target material, unless monoisotopic or denoted otherwise.
c: I_{β^+} value has rather large uncertainty.
d: Experimental value.

Small amounts of ^{64}Cu can also be produced using the deuteron induced reactions on ^{64}Zn and ^{nat}Zn [*cf.* 51,52]. Due to extensive demand for this radionuclide for radioimmunotherapy, attempts are underway to commercialize its production.

The radionuclide **^{124}I** is both a diagnostic and a therapeutic agent. It was originally produced *via* the ^{124}Te$(d,2n)^{124}$I reaction [53]; accurate cross section data were measured later [54]. Several other reactions have also been investigated [*cf.* 20–24]. However, due to the high level of the ^{125}I ($T_{1/2} = 60.0$ d) impurity associated with those processes, the method ^{124}Te$(p,n)^{124}$I suggested by our group [19], was found to be more suitable. With this process the ^{125}I impurity level is < 0.1%. Today almost all the laboratories use this method [*cf.* 55–58]. It involves irradiation of a $^{124}TeO_2$ target and removal of radioiodine by a dry distillation process [*cf.* 30]. The yield is rather low and the product is somewhat expensive. Nonetheless, due to increasing demands for this radionuclide, efforts are underway to produce this radionuclide in larger qunatities.

The production of **^{86}Y** was also investigated in detail at Jülich and the reaction ^{86}Sr$(p,n)^{86}$Y was found to be the most suitable [17,36,37]. The irradiated $^{86}SrCO_3$ target was dissolved in a small volume of conc. HCl and the separation of radioyttrium was carried out, as mentioned above, by coprecipitation followed by ion-exchange [36]; later in combination with HPLC [37]. Four other methods of separation have also been applied: one involves electrolysis [59,90,91], the other one multiple column chromatography [60], the third one solvent extraction [*cf.* 61], and the fourth one a simple precipitation of the target material [62,92]. The electrolytic method appears to be more promising. The radionuclide ^{86}Y obtained has a purity of about 99%. The target material ^{86}Sr is recovered easily and, since the suggested proton energy of 14 MeV is below the threshold of the ^{86}Sr$(p,pn)^{85}$Sr reaction, the recovered target material is

free of any radioactive impurity. In contrast, the intermediate energy reactions used for the production of ^{86}Y, *e.g.* ^{87}Sr$(p, 2n)^{86}$Y and ^{88}Sr$(p, 3n)^{86}$Y reactions, lead to high ^{87}Y impurity (see below).

The radionuclide ^{86}Y has become the most suitable positron emitter for quantification of radiation dosimetry of ^{90}Y-labelled therapeuticals. The demand for this radionuclide is also increasing and so its large scale production is being planned at several centres.

3.2 Production using intermediate energy reactions

Despite the above discussed capability of low-energy nuclear reactions on highly enriched target isotopes to produce many novel positron emitters there are some radionuclides which can be produced exclusively or alternatively using intermediate-energy reactions. A list of those radionuclides is given in Table 2 [*cf.* 93–122]. Some of the examples are: ^{56}Fe$(p, 2n)^{55}$Co, ^{76}Se$(p, 2n)^{75}$Br, ^{111}Cd$(p, 2n)^{110g}$In, ^{125}Te$(p, 2n)^{124}$I, ^{40}Ar$(p, 3n)^{38}$K, ^{75}As$(p, 3n)^{73}$Se, ^{79}Br$(p, 3n)^{77}$Kr, ^{85}Rb$(p, 3n)^{83}$Sr, ^{122}Te$(p, 3n)^{120g}$I, ^{55}Mn$(p, 4n)^{52}$Fe and ^{68}Zn$(p, \alpha n)^{64}$Cu. The $(p, 2n)$ reaction can generally be performed at a 30 MeV cyclotron. For other reactions, higher proton energies, in some cases up to 100 MeV, are needed. With the emission of a large number of nucleons, the nuclear data work becomes rather extensive. As a typical example, the excitation functions of several measured reactions in the interaction of protons with ^{85}Rb [123] are shown in Fig. 7. Evidently, for the production of a desired radionuclide, a narrow energy window has to be chosen. In the example given above, the suitable energy range for the production of the novel positron emitter ^{83}Sr amounts to $E_p = 38 \rightarrow 30$ MeV. Similarly, the radionuclide ^{82}Sr (the parent nuclide used in the preparation of the standard ^{82}Sr/^{82}Rb generator system) is advantageously produced over the energy range of $E_p = 70 \rightarrow 50$ MeV.

Although in the intermediate energy region mostly protons are available and are also preferably used, other charged particles like deuterons, ^{3}He- and α-particles may also induce a few useful reactions. For example, the intermediate energy deuterons could be useful in the production of ^{64}Cu *via* the ^{nat}Zn(d, x)-process [100, 101] and ^{73}Se *via* the ^{75}As$(d, 4n)$-reaction [102]. Similarly, ^{75}Br and ^{76}Br are still produced *via* the ^{75}As$(^3$He$, 3n)^{75}$Br and ^{75}As$(^3$He$, 2n)^{76}$Br reactions, respectively, because of the difficulty in target construction while using enriched ^{76}Se. In some other cases, *e.g.* ^{52}Fe, ^{77}Kr, ^{83}Sr, ^{86}Y and ^{94m}Tc, the use of the ^{3}He-particle beam is optional, the yield being lower than that using the corresponding (p, xn) reaction. As far as the α-particle beam is concerned, to date the radionuclides ^{30}P and ^{38}K have been exclusively produced in GBq amounts by an (α, n) reaction [*cf.* 124, 125]. In case of non-availability of 40 MeV protons, the utility of the ^{70}Ge$(\alpha, n)^{73}$Se reaction in the production of ^{73}Se in GBq amounts has also been demonstrated [31]. The use of the ^{nat}Cu$(\alpha, x)^{66}$Ga and ^{nat}Sr$(\alpha, x)^{89}$Zr reactions to produce ^{66}Ga and ^{89}Zr is again optional [115, 133], since the yields of the commonly used ^{66}Zn$(p, n)^{66}$Ga and ^{89}Y$(p, n)^{89}$Zr processes are much higher. The possibility of production of ^{82}Sr *via* the ^{82}Kr$(\alpha, 4n)^{82}$Sr reaction has also been investigated [126]. Though less effective, it could be an alternative method to the ^{85}Rb$(p, 4n)^{82}$Sr process if the available proton energy is below 70 MeV. Very recently the ^{123}Sb$(\alpha, 3n)^{124}$I reaction was carefully studied [122] and it was concluded that irradiation of ^{123}Sb with 45 MeV α-particles, especially in a parasitic position, could lead to appreciable quantities of the radionuclide ^{124}I.

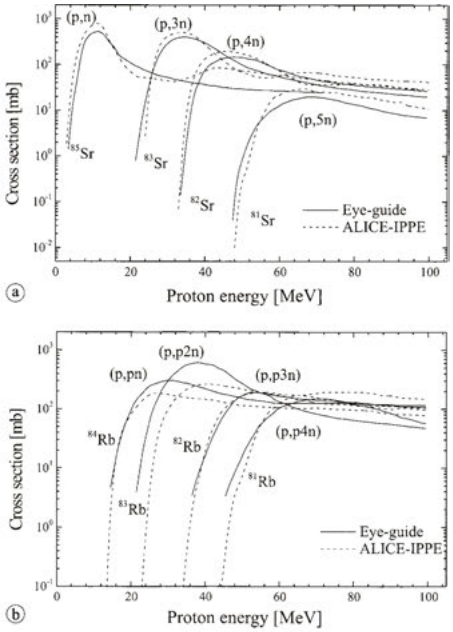

Fig. 7. Excitation functions of proton induced nuclear reactions on ^{85}Rb. **(a)** ^{85}Rb(p, xn)-reactions leading to the formation of the radionuclides ^{85}Sr, ^{83}Sr, ^{82}Sr and ^{81}Sr. **(b)** ^{85}Rb(p, pxn)-reactions giving rise to the radionuclides ^{84}Rb, ^{83}Rb, ^{82}Rb and ^{81}Rb. The experimental data [112, 123] are shown as eye-guide solid curves and the results of calculations using the nuclear reaction model code ALICE-IPPE [123] as dotted curves. With increasing projectile energy the number of radioactive products formed increases considerably.

The above discussion shows that intermediate energy cyclotrons have great potential for production of novel positron emitters. For most of the listed radionuclides, sufficient quantities for medical applications have been produced. However, a critical look at the various processes is necessary. The radionuclides ^{30}P and ^{38}K are short-lived and can only be locally used. The radionuclides ^{52}Mn, ^{55}Co, ^{64}Cu, ^{66}Ga, ^{76}Br, ^{86}Y, ^{89}Zr, ^{94m}Tc and ^{120g}I produced *via* intermediate energy reactions (*cf.* Table 2 and also Refs. [127–130]) often contain larger radionuclidic impurities than in the case of low-energy production reactions, so that their preferred routes are those given in Table 1. This has been clearly demonstrated in the case of ^{55}Co, ^{86}Y and ^{120g}I. Whereas the ^{56}Fe$(p, 2n)^{55}$Co [98], ^{88}Sr$(p, 3n)^{86}$Y [116] and ^{122}Te$(p, 3n)^{120g}$I [12] reactions give much higher yields of the products than the low-energy

Table 2. Novel PET radionuclides produced using intermediate energy cyclotrons.

Radio-nuclide	Decay data[a]				Production data				Reference
	$T_{1/2}$	I_{β^+} [%]	E_{β^+} [keV]	E_γ [keV (%)]	Common production route	Energy range [MeV]	Calculated yield [MBq/μA h]	Radionuclidic impurity (%)	
^{30}P	2.5 min	99.9	3245	2235 (0.06)	^{27}Al(α, n)	28 → 10	740	–	[93]
^{38}K	7.6 min	99.4	2724	2168 (99.9)	^{35}Cl(α, n)	22 → 7	270	–	[94]
					^{40}Ar(p, $3n$)	39 → 23	550	–	[95]
^{52}Mn	5.6 d	29.6	576	1434 (100) 935 (94)	^{52}Cr(^{3}He, t)	36 → 10	5.6	^{54}Mn (0.8)	[96]
^{52}Fe	8.3 h	55.5	806	169 (99.2)	^{55}Mn(p, $4n$)	100 → 60	22	^{55}Fe (< 2)	[97]
					^{52}Cr(^{3}He, $3n$)	36 → 17	1.3	^{55}Fe (< 0.01)	[96]
^{55}Co	17.6 h	76.0	1498	931 (75) 477 (20)	^{56}Fe(p, $2n$)	32 → 18	130	^{56}Co (2)	[98]
^{64}Cu	12.7 h	17.8	653	1346 (0.53)	^{68}Zn(p, αn)[b]	30 → 21	116	^{67}Cu (< 0.1)	[99]
					^{nat}Zn(d, x)	25 → 10	57	^{67}Cu (< 1)	[100, 101]
^{66}Ga	9.5 h	56[c]	4153	1039 (38) 2752 (23.8)	^{nat}Cu(α, x)	20 → 10	33	^{67}Ga (1.2)	[133]
^{73}Se	7.1 h	65.4	1651	67 (70) 361 (97)	^{75}As(p, $3n$)	40 → 30	1.4×10^3	^{72,75}Se (< 0.2)	[102]
					^{75}As(d, $4n$)	45 → 33	650	^{72,75}Se (< 0.3)	[102]
					^{nat}Ge(^{3}He, xn)	36 → 13	37	^{72,75}Se (2.0)	[103]
					^{nat}Ge(α, xn)	28 → 13	26	^{72,75}Se (1.0)	[103]
					^{nat}Br(p, x)	63 → 42	81	^{75}Se (1.2)	[104]
^{75}Br	1.6 h	73	2008	286 (92)	^{75}As(^{3}He, $3n$)	36 → 25	278	^{76}Br (1.7)	[105]
					^{76}Se(p, $2n$)[b]	24 → 21	1.2×10^3	^{76}Br (2)	[106–108]
					^{77}Se(p, $3n$)[b]	60 → 40	2×10^3	^{76}Br (25)	[108]
^{76}Br	16.0 h	58.2	3941	559 (74) 657 (15.9) 1854 (14.7)	^{75}As(^{3}He, $2n$)	18 → 10	11	^{77}Br (1.6)	[105]
					^{77}Se(p, $2n$)[b]	66 → 14	1.3×10^3	^{77}Br (< 15)	[108]
^{77}Kr	1.2 h	84	2041	130 (80) 146 (38)	^{77}Se(^{3}He, $3n$)[b]	36 → 15	425	^{76,79}Kr (0.7)	[109]
					^{79}Br(p, $3n$)[b]	40 → 30	7.4×10^3	^{79}Kr (< 1)	[110]
^{81}Rb	4.6 h	27[c]	1026	190 (64.3) 446 (23.3)	^{82}Kr(p, $2n$)[b]	27 → 19	1.8×10^3	^{82m}Rb (7)	[111]
^{83}Sr	32.4 h	26[c]	1254	763 (30) 381 (19.6)	^{85}Rb(p, $3n$)[b]	37 → 30	160	^{85}Sr (0.2)	[112]
					^{82}Kr(^{3}He, $2n$)[b]	18 → 10	5	^{82}Sr (0.2)	[113]
^{86}Y	14.7 h	33[c]	2019	1077 (82.5) 628 (32.6) 1153 (30.5)	^{nat}Rb(^{3}He, xn)	24 → 12	190	^{87}Y (12)	[17]
					^{88}Sr(p, $3n$)[b]	42 → 30	1.0×10^3	^{87}Y (10.0)	[114, 116]
^{89}Zr	78.4 h	22.3	897	909 (100)	^{nat}Sr(α, x)	20 → 8	0.9	^{88}Zr (0.6)	[115]
^{94m}Tc	52 min	72.0	2470	871 (94.2)	^{93}Nb(^{3}He, $2n$)	18 → 10	33	^{94g}Tc (25)	[117]
					^{92}Mo(α, d)[b]	26 → 18	98	^{94g}Tc (30)	[118]
^{110g}In	1.1 h	62[c]	2300	658 (98)	^{110}Cd(^{3}He, x)[b]	36 → 25	81	^{111g}In (< 0.8)	[119]
					^{111}Cd(p, $2n$)[b]	23 → 16	6×10^3	^{110m}In (10)	[120]
^{120g}I	1.3 h	56.0	4593	560 (73) 1522 (11.2)	^{122}Te(p, $3n$)[b]	37 → 32	3.6×10^3	^{120m}I (25)	[12]
^{124}I	4.18 d	22.0	2137 1691 (10.4) 723 (10.0)	603 (61)	^{125}Te(p, $2n$)[b]	22 → 15	93	^{125}I (0.7)	[121]
					^{123}Sb(α, $3n$)[b]	45 → 30	16	^{125,126}I (2.5)	[122]

a: Decay data were mostly taken from ENSDF. For ^{64}Cu, ^{76}Br, ^{120g}I and ^{124}I the I_{β^+} values were adopted from Refs. [25, 26].
b: Using highly enriched isotope as target material.
c: I_{β^+} value has rather large uncertainty.

^{54}Fe(d, n)^{55}Co, ^{86}Sr(p, n)^{86}Y and ^{120}Te(p, n)^{120g}I reactions, respectively, the level of the ^{56}Co impurity in ^{55}Co, of ^{87}Y in ^{86}Y and of ^{120m}I in ^{120g}I is much higher. On the other hand, the production of the radionuclides ^{52}Fe, ^{73}Se, ^{77}Kr and ^{83}Sr demands a high intensity cyclotron, accelerating protons up to about 70 MeV (in the case of ^{52}Fe preferably up to 100 MeV). Furthermore, the production of ^{124}I *via* the ^{125}Te(p, $2n$)-reaction deserves more attention. The ^{125}I-impurity level of 0.7% in this process [121] is higher than that of < 0.1% in the ^{124}Te(p, n)-process [19], but the yield of ^{124}I is by a factor of about six higher. Thus more efforts need to be invested in intermediate energy reactions to make better use of production possibilities of some novel positron emitters.

3.3 Production of novel parent generator radionuclides

Two standard positron emitters, namely ^{68}Ga ($T_{1/2} = 68$ min) and ^{82}Rb ($T_{1/2} = 1.3$ min) are routinely available *via* the generator systems ^{68}Ge(271 d)/^{68}Ga and ^{82}Sr(25.3 d)/^{82}Rb (see Introduction). For production of the parent radionuclide, a high intensity intermediate energy accelerator is needed. Presently the supply of both ^{68}Ge and ^{82}Sr appears to be adequate. However, due to enhancing interest in ^{68}Ga-radiopharmaceuticals, more efforts related to ^{68}Ge production and an efficient generator column preparation may soon be called for. Furthermore, since the half-life of ^{68}Ga is not very short, its direct pro-

Table 3. Production of novel positron emitters *via* generator systems.

Parent nuclide ($T_{1/2}$)	Decay data of daughter					Production method of parent	Energy range [MeV]	Theor. yield of parent [MBq/μA h]	Reference
	Nuclide	$T_{1/2}$	$I_{\beta+}$ [%]	$E_{max\ \beta+}$ [keV]	E_γ [keV (%)]				
^{44}Ti (60.4 a)	^{44}Sc	3.9 h	94.3	1474	1157 (99.9)	^{45}Sc(p, 2n)	32 → 18	~ 3 × 10^3	[141]
^{52}Fe (8.3 h)	^{52m}Mn	21 min	95.0	2633	1434 (98.2)	^{55}Mn(p, 4n)	100 → 60	22	[97]
						^{52}Cr(^{3}He, 3n)	36 → 17	1.3	[96]
^{62}Zn (9.1 h)	^{62}Cu	9.7 min	97.4	2926	1173 (0.34)	^{nat}Cu(p, xn)	30 → 18	230	[133]
						^{nat}Zn(p, x)	70 → 30	700	[134]
^{72}Se (8.5 d)	^{72}As	26.0 h	87.8	3334	834 (79.5)	^{75}As(p, 4n)	45 → 35[a]	8	[102]
						^{75}As(d, 5n)	55 → 40	7	[102]
						^{nat}Ge(^{3}He, xn)	36 → 10	0.7	[103]
^{122}Xe (20.1 h)	^{122}I	3.6 min	77.0	3100	564 (18)	^{127}I(p, 6n)	65 → 43	230	[135]
						^{124}Xe(p, 3n)	43 → 35	500	[136]
^{140}Nd (3.4 d)	^{140}Pr	3.4 min	51.0	2366	1596 (0.5)	^{141}Pr(p, 2n)	30 → 15	210	[139]
						^{nat}Ce(^{3}He, xn)	35 → 20	12	[139]

a: The production process was investigated only up to 45 MeV.

duction *via* the ^{68}Zn(p, n)-reaction is also gaining some importance.

Some other generator systems have also been proposed (for a review of production routes *cf*. [131, 132]). A few interesting systems for furnishing some novel positron emitters are listed in Table 3. They are discussed in some detail below. The systems ^{52}Fe/^{52m}Mn, ^{62}Zn/^{62}Cu and ^{122}Xe/^{122}I were proposed rather long time ago. Out of those, more detailed studies have been carried out only on the system ^{62}Zn/^{62}Cu. In general not much progress has been reported regarding their further applications. This is mainly due to the short half-lives of the parents, combined with the difficulties in their production. Although the ^{62}Zn parent nuclide can be produced with 30 MeV protons [*cf*. 133], the production of ^{52}Fe and ^{122}Xe demands higher energies [97, 135, 136]. Another reason for the limited use of those systems is the relatively short half-life of the daughter positron emitter.

The generator systems ^{72}Se/^{72}As and ^{140}Nd/^{140}Pr have great potential, the former for studying the biological behaviour of arsenic and the latter as an *in vivo* generator, if the Auger electron emitter ^{140}Nd is used in endoradiotherapy. The yield of the parent radionuclide ^{72}Se is rather low [*cf*. 102, 103]. Nonetheless two generator systems for obtaining the daughter ^{72}As, one based on distillation [137] and the other one on solid phase extraction [138] have been developed. With regard to ^{140}Nd, the (p, 2n) and (^{3}He, xn) reactions on ^{141}Pr and ^{nat}Ce, respectively, have been investigated in detail [*cf*. 139]. As expected, the former reaction leads to a much higher yield. A generator system based on physico-chemical transitions in ^{140}Pr complexes has also been described [*cf*. 140].

The generator system ^{44}Ti/^{44}Sc has received some attention in recent years. Due to the long half-life of 60.4 years of the parent, it is rather difficult to produce. Furthermore, there may be some regulatory problems in the introduction of this very long-lived system. Nonetheless, from the scientific and application point of view (see below), it appears worthwhile to develop it further. The suggested production reaction is ^{45}Sc(p, 2n)^{44}Ti and the excitation function, recently measured [141], is reproduced in Fig. 8. Evidently the cross section is not very high, which is qualitatively understandable, because the emission of two

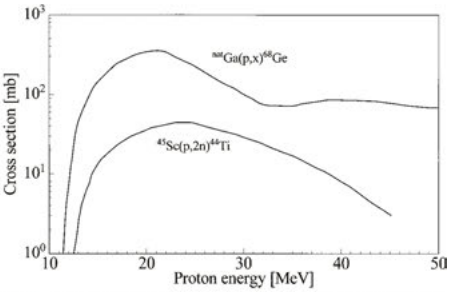

Fig. 8. Comparison of excitation functions of the nuclear reactions ^{45}Sc(p, 2n)^{44}Ti and ^{nat}Ga(p, xn)^{68}Ge used to induce the parent activities for preparation of the radionuclide generator systems ^{44}Ti/^{44}Sc and ^{68}Ge/^{68}Ga. The data for the former reaction are reproduced from Ref. [141] and those for the latter from Ref. [142].

neutrons in the interaction of a proton with a relatively light mass nucleus, such as ^{45}Sc, is not very favoured. For comparison the excitation function of the ^{nat}Ga(p, xn)^{68}Ge reaction [*cf*. 142] is also shown in Fig. 8. The first peak at about 21 MeV is attributed to the ^{69}Ga(p, 2n)^{68}Ge reaction and the second increase beyond 35 MeV is due to the contribution from the ^{71}Ga(p, 4n)^{68}Ge process. The excitation function for the formation of ^{68}Ge has a slightly lower threshold and an order of magnitude higher cross section than the ^{45}Sc(p, 2n)^{44}Ti reaction. Thus there is little analogy between the two reactions. The production of ^{68}Ge is routinely done. In the case of ^{44}Ti, to date a 185 MBq generator has been reported [143] and some post-elution purification of ^{44}Sc has been described [144]. Higher current targetry and long irradiation periods will be called for to obtain higher yields.

4. Applications of novel positron emitters

The applications of novel positron emitters are manifold [*cf*. 4]. A detailed discussion is beyond the scope of this

article; therefore, only the three major areas of application are briefly mentioned.

1. Study of slow metabolic processes, *e.g.* protein synthesis, cell proliferation, *etc.*.
2. Quantification of SPECT-radiopharmaceuticals.
3. Quantification of targeted therapy.

Some of the important positron emitters under the first category are ^{52}Fe ($T_{1/2} = 8.3$ h), ^{55}Co ($T_{1/2} = 17.6$ h), ^{72}As ($T_{1/2} = 26.0$ h), ^{73}Se ($T_{1/2} = 7.1$ h), and ^{124}I ($T_{1/2} = 4.18$ d). When attached to proper organic compounds, they could be used for detection of tumor, neuronal damage or organ functional deficiency. The slow uptake kinetics by an organ can be conveniently and quantitatively followed using a longer lived positron emitter and positron emission tomography.

With regard to quantification of SPECT-radiopharmaceuticals, an analogue approach is needed, which involves the use of a positron emitting nuclide of the chemical element of the SPECT radionuclide. Thus for quantification of a ^{99m}Tc-radiopharmaceutical, labelling can be done using the positron emitting radionuclide ^{94m}Tc ($T_{1/2} = 52$ min) followed by a PET measurement. This way the ^{99m}Tc-based SPECT flow agent terboroxime (CardioTec) was labelled with ^{94m}Tc for quantitative PET investigation [*cf*. 145], Similarly, ^{94m}Tc has been applied in studies related to changes in dopamine transporter concentrations (*e.g.* with TRODAT-1) [146].

A very significant application of non-standard longer lived positron emitters is in therapy planning. Since dosimetry in endotherapy with purely β^- emitting radionuclides like ^{90}Y ($T_{1/2} = 2.7$ d) has a rather large uncertainty, a mixture of the β^+ emitting ^{86}Y ($T_{1/2} = 14.7$ h) and the therapeutic radionuclide ^{90}Y was used [147]. The uptake kinetics were determined by PET imaging of ^{86}Y, and the results were used in an accurate dosimetric calculation. This concept is now finding increasing application. Another radionuclide investigated is ^{83}Sr ($T_{1/2} = 32.2$ h) which can be combined with the purely β^- emitting therapeutic radionuclide ^{89}Sr ($T_{1/2} = 50.0$ d). The dosimetry in the case of the most commonly used therapeutic radionuclide ^{131}I ($T_{1/2} = 8.0$ d) is fairly well established. However, if a PET study using ^{124}I precedes the use of ^{131}I, the dosimetric calculations can be done even more precisely. A further advantage of ^{124}I is that it could itself be used as a therapeutic agent. Because of the combination of PET and endoradiotherapy, allowing precise dosimetry, this radionuclide is superior to the commonly used reactor radionuclide ^{131}I. The cost of ^{124}I, however, is higher than that of ^{131}I.

In recent years, the importance of metallic positron emitters in quantification of radioimmunotherapy has been increasing. Radionuclides such as ^{67}Cu ($T_{1/2} = 2.6$ d), ^{67}Ga ($T_{1/2} = 3.3$ d) and ^{111}In ($T_{1/2} = 2.8$ d) can be attached to monoclonal antibodies (mAB) leading to therapeutic effects through interactions of β^- particles or Auger electrons with the tissue. The use of the respective positron emitting radionuclides ^{64}Cu ($T_{1/2} = 12.7$ h), ^{68}Ga ($T_{1/2} = 67.6$ min) and ^{110g}In ($T_{1/2} = 1.1$ h) allows PET imaging for quantification purposes. In particular, the radionuclide ^{64}Cu (with multiple decay mode) has proved to be very suitable for combining PET imaging and targeted therapy [*cf*. 148].

5. Conclusions and perspectives

Radionuclide production technology at cyclotrons has been well developed, especially for short-lived organic positron emitters. In this regard, all components of the technology, *i.e.*, special purpose cyclotron, high current irradiation target and automated or remotely controlled chemical processing unit can now be commercially purchased. Furthermore, two radionuclide generator systems providing short-lived positron emitters (^{68}Ga and ^{82}Rb) are supplied by several companies, though the parent nuclides are produced through intermediate energy nuclear reactions only at a few large research centres.

In contrast to the commonly used positron emitters, a few other longer lived positron emitting radionuclides, having passed the stage of laboratory scale production and clinical evaluation, are now in great demand, but are not easily available. A few examples are ^{64}Cu, ^{86}Y and ^{124}I. They are produced using highly enriched target material but low energy cyclotrons, whereby the radionuclidic purity is high but the yield is low. Efforts are therefore underway in commercially oriented laboratories to increase the production yields of those radionuclides and thus to ensure their availability on a broader scale.

The number of positron emitters potentially interesting for medical applications is relatively large. They are research type radionuclides and the development work needed is rather heavy, calling for investigations in many directions, starting from nuclear data measurements, proceeding through high current target construction and chemical processing, and leading up to quality control of the final product. Similar to the three novel positron emitters mentioned above, in many cases a combination of isotopically enriched target material and a small-sized cyclotron may be sufficient for production. However, for production of many new nuclides high intensity intermediate energy cyclotrons have great potential. This appears to be particularly true for metallic positron emitters used in combination with a longer lived β^- emitter or Auger electron emitter for radioimmunotherapy. The four pairs, namely ^{44}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{68}Ga/^{67}Ga and ^{110g}In/^{111}In, could be developed further with the availability of a new generation high power accelerator having proton energies up to 100 MeV. In general it is concluded that the field of cyclotron production of medical radionuclides is flourishing and that many new impulses are expected within the next few years, especially with regard to the use of novel positron emitters and therapeutic radionuclides.

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Appendix VI

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The present and future of medical radionuclide production

By S. M. Qaim*

Institut für Neurowissenschaften und Medizin, INM-5: Nuklearchemie, Forschungszentrum Jülich GmbH, 52425 Jülich, Germany

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Reactor and cyclotron production of medical radionuclides / γ-ray emitters for SPECT / Positron emitters for PET / Corpuscular radiation emitters for internal radiotherapy / Low and intermediate energy nuclear reactions / Radionuclide generators / Future directions

Summary. Medical radionuclide production technology is well established. Both reactors and cyclotrons are utilized for production; the positron emitters, however, are produced exclusively using cyclotrons. A brief survey of the production methods of most commonly used diagnostic and therapeutic radionuclides is given. The emerging radionuclides are considered in more detail. They comprise novel positron emitters and therapeutic radionuclides emitting low-range electrons and α-particles. The possible alternative production routes of a few established radionuclides, like ^{68}Ga and ^{99m}Tc, are discussed. The status of standardisation of production data of the commonly used as well as of some emerging radionuclides is briefly mentioned. Some notions on anticipated future trends in the production and application of radionuclides are considered.

1. Introduction

Radioactivity is unique in the sense that, in spite of its hazardous nature, it finds application in medicine both in diagnosis and therapy [*cf*. 1]. Each application, however, demands a special type of radionuclide. For *in vivo* diagnostic investigations involving organ imaging, for example, radionuclides are required that can be efficiently detected from outside of the body. To this end, short-lived γ-ray emitters, like ^{99m}Tc and ^{123}I, and positron emitters, like ^{11}C and ^{18}F, are commonly used, the former finding application in Single Photon Emission Computed Tomography (SPECT) and the latter in Positron Emission Tomography (PET). The underlying principle in diagnostic nuclear medicine is that the radiation dose to the patient is as low as possible, compatible with the required quality of imaging and the diagnostic advantage in comparison to non-radioactive methods. Thus a complete set of decay data of a radionuclide is required to be able to calculate the radiation dose which plays a very important role in its choice for a diagnostic medical application.

*E-mail: s.m.qaim@fz-juelich.de.
Co-ordinating Editor of the Journal.

The therapeutic application of radioactivity involves either external radiation therapy or internal radiotherapy. Whereas for the former, radionuclides emitting energetic β^- particles or hard γ-rays are commonly used, for example ^{60}Co ($T_{1/2} = 5.27$ a), ^{137}Cs ($T_{1/2} = 30.17$ a) and ^{192}Ir ($T_{1/2} = 73.8$ d), the spectrum of radionuclides required in internal radionuclide therapy (endotherapy) is very broad. Since in this case a localised, well-defined radiation dose needs to be deposited in a malignant or inflammatory tissue, radionuclides emitting low-range highly-ionising radiation, *i.e.* α or β^- particles, conversion and/or Auger electrons, are of great interest.

The medical radionuclide production technology is well developed and is pursued both at commercial centres and some nuclear science research institutes. However, besides routine production and medical application of radionuclides, constant research work is going on around the world to improve the existing production methodologies of some established radionuclides as well as to develop novel radionuclides for new medical applications. Some thoughts and efforts are also constantly devoted to future development of this technology to meet the challenges of new approaches in medical investigations.

The production of radionuclides is carried out using nuclear reactors [for reviews *cf*. 2, 3] and accelerators/cyclotrons [for a review *cf*. 4]. The reactor production generally leads to neutron excess radionuclides. They mostly decay by β^- emission and are therefore especially suitable for radiotherapy. The cyclotron produced radionuclides, on the other hand, are mainly neutron deficient and decay by electron capture (EC) or β^+ emission. They are therefore particularly useful for diagnostic studies. The positron emitters can be produced only at cyclotrons. For production of some nuclides both nuclear reactors and cyclotrons are extensively used. In other words, their roles are to be regarded as complementary. Worldwide there exist about 400 research reactors and about 500 cyclotrons. Most of them are at least partly used for production of medically useful radionuclides. The radionuclide production technology today has thus become an integral part of modern nuclear medicine and its future prospects also appear to be bright.

This article deals with three aspects of medical radionuclide production technology. In the first part, the routine production for state-of-the-art patient care is briefly outlined; in the second, the on-going new developments are discussed in some detail; and in the third, some emerging thoughts

relevant to the future perspectives of this technology are considered.

2. Present status of radionuclide production technology

The radionuclides commonly used in medicine and in drug development are listed in Table 1, together with their decay properties and production routes [*cf*. 1, 5]. They are divided in four groups depending on the function they serve. Each group is discussed below.

2.1 Soft β^- emitters for *in vitro* studies

In this group the most important radionuclides include ^{3}H ($T_{1/2} = 12.3$ a), ^{14}C ($T_{1/2} = 5730$ a) and ^{125}I ($T_{1/2} = 59.4$ d). They are available in large quantities in all parts of the world. Over the last 60 years, the radionuclides ^{3}H and ^{14}C have played a very important role in biochemistry for enhancing our understanding of physiological functions of molecules and radiopharmaceuticals (drug development research). This was possible due to the relatively simple method of measurement of their radioactivity *via* liquid scintillation counting. The radionuclide ^{125}I with its low-energy emissions is very well suited for autoradiography and is commonly used in radioimmunoassay or receptor binding studies.

All the three radionuclides mentioned above are produced in a nuclear reactor: Tritium *via* the $^{6}Li(n, \alpha)$-reaction on a Li or LiF target, ^{14}C through the $^{14}N(n, p)$-reaction on an AlN target, and ^{125}I using the $^{124}Xe(n, \gamma)^{125}Xe \rightarrow {}^{125}I$ process by irradiating ^{nat}Xe or enriched ^{124}Xe filled in an Al-capsule. Tritium is generally available as tritium gas or tritiated water, ^{14}C as $^{14}CO_2$ or $Ba^{14}CO_3$, and ^{125}I as $^{125}I^-$.

In addition to the three major soft β^- emitting radionuclides mentioned above, two other soft β^- emitting nuclides, namely ^{33}P ($T_{1/2} = 25.3$ d; $E_{\beta^-} = 248$ keV) and ^{35}S ($T_{1/2} = 87.5$ d; $E_{\beta^-} = 167$ keV), also find some limited application involving *in vitro* investigations. Both are produced in the no-carrier-added form in a high fast flux nuclear reactor, the former *via* the $^{33}S(n, p)^{33}P$ reaction on isotopically enriched ^{33}S and the latter through the $^{35}Cl(n, p)^{35}S$ reaction on a KCl target [*cf*. 6]. The radionuclides ^{33}P and ^{35}S are generally available as $H_3{}^{33}PO_4$ and $H_2{}^{35}SO_4$, respectively, besides other forms.

2.2 Gamma emitters for SPECT

The number of γ-ray emitters which have found some application in imaging using gamma cameras is relatively large. However, with the advent of SPECT tomographs, it became incumbent to use radionuclides emitting either only one γ-ray or at least one predominant γ-ray within the energy range of 100–200 keV. The choice was thus reduced to five radionuclides, namely ^{67}Ga ($T_{1/2} = 3.26$ d), ^{99m}Tc ($T_{1/2} = 6.0$ h), ^{111}In ($T_{1/2} = 2.8$ d), ^{123}I ($T_{1/2} = 13.2$ h) and ^{201}Tl ($T_{1/2} = 3.06$ d). The radionuclide ^{99m}Tc is by far the most commonly used SPECT radionuclide. It ideally emits a 141 keV photon and causes the least radiation dose to the patient. It is almost always available in a clinic *via* the $^{99}Mo/^{99m}Tc$ generator system. Furthermore, by virtue of its versatile complex formation chemistry, labelling methods are established to rather easily bind it to various compounds. This characteristic has led to development of several robust labelling kits. The eluted ^{99m}Tc as pertechnetate is transferred to an ampoule containing an appropriate lyophilised mixture of reagents. On shaking, the labelling of given ligands with ^{99m}Tc occurs in a specific configuration and the product is then ready for human use. Also the radionuclide ^{123}I is commonly used. However, due to its lesser availability and higher cost, ^{123}I is much less broadly used than ^{99m}Tc. The third radionuclide, *viz*. ^{201}Tl, is extensively used for myocardial perfusion measurements. The remaining two radionuclides, namely ^{67}Ga and ^{111}In are less commonly used as SPECT agents. They are partly being considered for therapeutic applications because they emit a large number of Auger electrons.

As mentioned above, ^{99m}Tc is available *via* the $^{99}Mo/^{99m}Tc$ generator. An Al_2O_3-column is loaded with ^{99}Mo and the daughter activity is periodically removed by elution with saline. The parent nuclide ^{99}Mo ($T_{1/2} = 66.0$ h) is produced at a nuclear reactor, and two routes are possible: $^{98}Mo(n, \gamma)^{99}Mo$ and $^{235}U(n, f)^{99}Mo$. The cross section of the (n, γ)-reaction is relatively small and due to the use of ^{nat}Mo (with a ^{98}Mo content of 24.13%) as target material, the specific activity of the ^{99}Mo produced is low. Thus, because of the heavy loading of the Al_2O_3-generator column with stable molybdenum, in spite of the rather big dimensions of the column, the risk of breakthrough of Mo is high and ^{99m}Tc eluate volumes are large. Somewhat higher specific activity is achieved using a high-flux nuclear reactor. However, such reactors are seldom available for radionuclide production. Attempts have been made to enrich ^{99}Mo *via* a Szilard Chalmers process [*cf*. 7] but the separation yields are low. Furthermore, some gel and distillation generators have been developed [*cf*. 8, 9] but their overall efficiencies are not comparable to that of the alumina column generator. In view of the situation, combined with the fact that for production purposes irradiations are mostly done at medium-flux reactors, the method of choice for production of ^{99}Mo for medical use is the fission process.

The cross section for the thermal neutron induced fission of ^{235}U is 596 barn and the cumulative yield of ^{99}Mo is 6.16%; thus TBq amounts of ^{99}Mo can be produced per batch. Although the chemical processing of the irradiated target is very laborious, especially in view of the high demand on the quality assurance of the separated product, only the fission process is accepted because it leads to ^{99}Mo of very high specific activity. In fact the fission produced ^{99}Mo on an Al_2O_3 column is regarded as a gold standard generator system. The eluted ^{99m}Tc occurs as pertechnetate.

The ease and success associated with the generator elution of ^{99m}Tc and the development of kit formulation of some very important ^{99m}Tc-labelled diagnostic agents has led to the very wide use of ^{99m}Tc. The fission ^{99}Mo is produced only at a few advanced centres and is then distributed to various laboratories around the world where the generator loading is undertaken (*dispensing*). The generators are then sent to regional clinics. It is estimated that worldwide 35 million patients per year are subjected to diagnostic investigations with ^{99m}Tc [*cf*. 10]. Despite this success story and the demonstrated need for continuous availability of this radionuclide, its future supply appears to be somewhat

Table 1. Commonly used medical radionuclides and their production methods (decay data taken from www.nndc.bnl/nudat2/).

Radionuclide	$T_{1/2}$	Emitted radiation[a,b] (energy in keV)	Production process	Energy range [MeV]	Typical batch yield [GBq]
		Soft β^- emitters for *in vitro* studies			
^{3}H	12.3 a	β^-	^{6}Li(n, α)	*c*	> 500
^{14}C	5730 a	β^-	^{14}N(n, p)	*c*	20
^{125}I	59.4 d	Auger electrons (and X-rays)	^{124}Xe$(n, \gamma)^{125}$Xe → ^{125}I	*c*	50
		γ-emitters for SPECT			
^{67}Ga	3.26 d	γ (93) γ (185)	^{68}Zn$(p, 2n)^{67}$Ga	26 → 18	50
^{99}Mo (generator) ↓	2.75 d	β^-	^{235}U$(n, f)^{99}$Mo	*c*	> 10^3
^{99m}Tc	6.0 h	γ	^{98}Mo$(n, \gamma)^{99}$Mo	*c*	10
^{123}I	13.2 h	γ	^{123}Te(p, n)	14.5 → 10	20
			^{124}Xe$(p, x)^{123}$Xe → ^{123}I	29 → 23	70[e]
			^{127}I$(p, 5n)^{123}$Xe → ^{123}I	65 → 45	70[e]
^{111}In	2.8 d	γ (173) γ (247)	^{112}Cd$(p, 2n)^{111}$In	25 → 18	50
^{201}Tl	3.06 d	X-rays (69–82) γ (166)	^{203}Tl$(p, 3n)^{201}$Pb → ^{201}Tl	28 → 20	50[f]
		Positron emitters for PET			
^{11}C	20.4 min	β^+	^{14}N(p, α)	13 → 3	100
^{13}N	10.0 min	β^+	^{16}O(p, α)	16 → 7	30
^{15}O	2.0 min	β^+	^{14}N(d, n)	8 → 0	100
			^{15}N(p, n)	10 → 0	50
^{18}F	110 min	β^+	^{18}O(p, n)	16 → 3	100
			^{20}Ne(d, α)	14 → 0	30
^{68}Ga	68.3 min	β^+	^{69}Ga$(p, 2n)^{68}$Ge ^{68}Ge → ^{68}Ga (generator)	22 → 13	5
^{82}Rb	1.3 min	β^+	^{nat}Rb$(p, x)^{82}$Sr ^{82}Sr → ^{82}Rb (generator)	70 → 50	40
		Therapeutic radionuclides β^- emitters			
^{32}P	14.3 d	β^-	^{32}S(n, p)	*d*	> 100
^{89}Sr	50.5 d	β^-	^{89}Y(n, p)	*d*	20
^{90}Y	2.7 d	β^-	^{235}U$(n, f)^{90}$Sr ^{90}Sr → ^{90}Y (generator)	*c*	20
^{131}I	8.0 d	β^-	^{130}Te$(n, \gamma)^{131m,g}$Te → ^{131}I	*c*	> 100
			^{235}U$(n, f)^{131}$I	*c*	> 100
^{153}Sm	1.9 d	β^-	^{152}Sm(n, γ)	*c*	> 100[g]
^{169}Er	9.4 d	β^-	^{168}Er(n, γ)	*c*	50[h]
^{177}Lu	6.7 d	β^-	^{176}Lu(n, γ)	*c*	50[g]
			^{176}Yb$(n, \gamma)^{177}$Yb → ^{177}Lu	*c*	50
^{188}Re	17.0 h	β^-	^{186}W$(n, \gamma)^{187}$W$(n, \gamma)^{188}$W ^{188}W → ^{188}Re (generator)	*d*	20
		α-emitter			
^{211}At	7.2 h	α	^{209}Bi$(\alpha, 2n)$	28 → 20	< 5
		X-ray and Auger electron emitters			
^{103}Pd	17.0 d	Auger electrons and X-rays	^{103}Rh(p, n)	13 → 7	50
^{125}I[i]	59.4 d	Auger electrons and X-rays	^{124}Xe$(n, \gamma)^{125}$Xe → ^{125}I	*c*	50

a: For β^-, β^+ and α-particles the values are maximum energies.
b: The γ-ray is used in SPECT studies. For PET studies annihilation radiation is used.
c: With reactor neutrons.
d: With neutrons in a high flux reactor.
e: ^{123}I yield after a 7 h decay of ^{123}Xe.
f: ^{201}Tl yield after a 32 h decay of ^{201}Pb.
g: Product of moderate specific activity.
h: Product of low specific activity.
i: This radionuclide is also listed above under soft β^- emitters for *in vitro* investigations.

jeopardised. On one hand the presently used reactors are ageing and there appears to be no planning for their replacement and, on the other, there is the risk of nuclear weapons' proliferation due to the use of highly enriched ^{235}U as the target material. Both these aspects demand a search for alternative methods of production and separation of ^{99}Mo and/or ^{99m}Tc. Considerable efforts are underway in this direction. They are discussed in detail below (Sect. 3.3).

For the production of the radionuclide ^{123}I, about 25 nuclear processes have been investigated [*cf*. 1]. Out of them only three are commonly used, mainly due to the level of the radionuclidic impurity associated with most of the processes. On a small cyclotron ($E < 20$ MeV) the reaction $^{123}Te(p, n)^{123}I$ over the energy range $E_p = 14.5 \rightarrow 10$ MeV is utilized, provided a highly enriched ^{123}Te-target is available. The yield of ^{123}I is, however, rather low. The separation of radioiodine is generally done *via* a dry distillation process [*cf*. 4].

The second method involves the production of the precursor ^{123}Xe ($T_{1/2} = 2.1$ h) which decays to ^{123}I. It demands a medium-sized cyclotron ($E \approx 30$ MeV). Starting with highly enriched ^{124}Xe gas as target material, the precursor ^{123}Xe is produced *via* the processes $^{124}Xe(p, 2n)^{123}Cs \rightarrow {}^{123}Xe$ and $^{124}Xe(p, pn)^{123}Xe$ [*cf*. 11]. Over the optimum energy range of $E_p = 29 \rightarrow 23$ MeV the major contribution to the formation of ^{123}I is furnished by the $(p, 2n)$ process. The level of the only radionuclidic impurity ^{121}I ($T_{1/2} = 2.1$ h) is negligibly small. However, if the incident proton energy exceeds 30 MeV, the cross section of the process $^{124}Xe(p, x)^{121}I$ becomes appreciable [*cf*. 12]. The latter decays to long-lived ^{121}Te ($T_{1/2} = 154$ d) which is a disadvantage. An energy control of the beam incident on the target is therefore mandatory. The activated xenon gas is allowed to decay for about 7 h and ^{123}I is then collected by rinsing the inner wall of the container. This method of production is now commonly used because it gives the purest product and is the only one accepted by regulations in most countries. The enriched target gas ^{124}Xe is relatively expensive. The technology related to irradiation and safe recovery of the target gas as well as an efficient removal of ^{123}I from the target wall is thus very demanding. This technology is, however, now commercially available.

The third method of production of ^{123}I utilizes the intermediate energy nuclear process $^{127}I(p, 5n)^{123}Xe \rightarrow {}^{123}I$, the optimum energy range being $E_p = 65 \rightarrow 45$ MeV. The product ^{123}Xe is removed from the NaI target, collected in a vessel and is allowed to decay for about 7 h. Thereafter ^{123}I is collected in a small volume by rinsing the inner wall of the vessel. This process leads to a high yield of ^{123}I but in this case the product contains about 0.25% ^{125}I ($T_{1/2} = 59.4$ d) as impurity.

The radioiodine produced by all the three methods occurs as iodide which is a suitable chemical form for subsequent labelling of organic compounds *via* substitution reactions.

The production of ^{201}Tl is mainly done *via* the route $^{203}Tl(p, 3n)^{201}Pb \rightarrow {}^{201}Tl$, utilizing the energy range $E_p = 28 \rightarrow 20$ MeV [*cf*. 4]. The irradiation of ^{nat}Tl or ^{203}Tl is done at a medium-sized cyclotron and the chemical processing follows in two steps: first the precursor ^{201}Pb ($T_{1/2} = 9.4$ h) is separated and, after its decay for 32 h, during which the maximum growth of ^{201}Tl occurs, the product is isolated as $^{201}TlCl$. It should be pointed out here that the target material thallium is toxic. The product ^{201}Tl, however, is in no-carrier-added form and can therefore be safely used, provided the stringent quality control standards are fully complied with. Furthermore, ^{201}Tl is useful only in the monovalent form; the trivalent form is not effective for medical application [*cf*. 4].

The above mentioned two less commonly used SPECT radionuclides, namely ^{67}Ga and ^{111}In, which are now also considered for Auger therapy (see below) are produced at a medium-sized cyclotron over the optimum energy range of $E_p = 25 \rightarrow 18$ MeV *via* the nuclear reactions $^{68}Zn(p, 2n)^{67}Ga$ and $^{112}Cd(p, 2n)^{111}In$, respectively [*cf*. 4]. In each case an enriched target is used and efficient methods of chemical purification have been worked out. The two radionuclides are commercially available in GBq amounts.

2.3 Positron emitters for PET

The number of positron-emitting radionuclides is large. For present day medical diagnostic imaging, the radionuclide used should have a short half-life, and emit only a low energy positron and possibly no high-energy γ-ray. Thus for routine PET investigations, mainly the short-lived organic positron emitters, *viz*. ^{11}C ($T_{1/2} = 20.4$ min) and ^{18}F ($T_{1/2} = 110$ min), and to a lesser extent ^{15}O ($T_{1/2} = 2$ min) and ^{13}N ($T_{1/2} = 10$ min), are used. The radionuclides ^{11}C, ^{13}N and ^{15}O are generally used at the site of production. ^{18}F, on the other hand, is extensively employed for transport to nearby medical units having a PET but not a cyclotron. They can all be produced at low-energy cyclotrons. Besides those four positron emitters, two other short-lived positron emitters, namely ^{68}Ga ($T_{1/2} = 67.6$ min) and ^{82}Rb ($T_{1/2} = 1.3$ min), widely used in diagnostic studies, are produced *via* generator systems. Their long-lived parents ^{68}Ge ($T_{1/2} = 271$ d) and ^{82}Sr ($T_{1/2} = 25.3$ d), respectively, are produced through intermediate energy reactions.

The organic positron emitters are generally produced using low-energy reactions [for reviews *cf*. 1, 13], *e.g.* ^{11}C *via* the $^{14}N(p, \alpha)$-reaction, ^{13}N through the $^{16}O(p, \alpha)$-reaction and ^{18}F using the $^{18}O(p, n)$-reaction. For ^{15}O production *via* the $^{14}N(d, n)$-reaction, and for electrophilic ^{18}F production *via* the $^{20}Ne(d, \alpha)$-reaction, of course a deuteron beam is needed. If it is not available, the radionuclide ^{15}O can be produced using the $^{15}N(p, n)$-reaction on highly enriched ^{15}N. On the other hand, for the production of ^{15}O, in a few PET centres a small single particle cyclotron ($E_d < 4$ MeV) has also been successfully utilized.

Regarding the technical aspects of production of short-lived positron emitters, considerable attention has been devoted over the last 25 years to high-current targetry and chemical processing. For production of ^{11}C and ^{15}O, for example, high-pressure gas targets have been developed, and the two radionuclides can be easily obtained in 100 GBq quantities. The chemical form of the product coming out of the target depends on the composition of the target gas and the accumulated radiation dose. Thus precursors for labelling work with ^{11}C comprise $^{11}CO_2$, $^{11}CH_4$ and increasingly ^{11}CO, and with ^{15}O it is $[^{15}O]O_2$. For the production of ^{11}C of high specific activity, special precautions are necessary since stable ^{12}C is present everywhere. The composition

of the target body material, the purity of the filling gas and the quality of the used chemicals must meet the recommended specifications [*cf*. 14]. For the production of ^{13}N and ^{18}F, generally water targets are used. In the former case, natural water ($H_2{}^{16}O$) is employed and the species obtained is $^{13}NO_3^-$; in the latter, enriched water ($H_2{}^{18}O$) is used and the species obtained is [$^{18}F^-$] fluoride. The radionuclide ^{18}F can now be produced in quantities up to 100 GBq per target batch.

As mentioned above, the production of the parent nuclides of the two commonly used generator-produced β^+ emitters, namely ^{68}Ga and ^{82}Rb, is done using intermediate energy reactions [*cf*. 15]. The radionuclide ^{68}Ge is basically produced *via* the $^{69}Ga(p, 2n)^{68}Ge$ reaction since the cross section is rather high (see discussion below). However, due to its long half-life, the yield is low and high proton beam fluxes approaching the mA level are essential. Furthermore, long irradiations are required. It is partly obtained *via* the spallation of bromine or arsenic; however, the purification of the product is cumbersome. Due to the increasing significance of the β^+ emitter ^{68}Ga (see discussion below), more concerted efforts are needed to ensure its continuous supply. The radionuclide ^{82}Sr is produced today mainly *via* the $^{nat}Rb(p, xn)$-process at $E_p = 70 \rightarrow 50$ MeV. A consortium of laboratories collaborates in irradiations but the chemical processing is mainly done at Los Alamos. The purified ^{82}Sr is then distributed worldwide to prepare generators. Recently the available generator has come to some disrepute because of the breakthrough of the long-lived radiostrontium. Efforts to remediate this drawback are underway.

In recent years, PET imaging has been gaining enhanced significance because it leads to quantitative information on regional physiological and pharmacological activities by a molecular probe (labelled with a positron emitter) with high sensitivity and with a spatial resolution down to 1 mm. The major impetus came through the production of ^{18}F in large quantities *via* the $^{18}O(p, n)^{18}F$ reaction [13, 16] at a small cyclotron followed by a simplified method of nucleophilic substitution by ^{18}F in organic molecules [17]. This led in particular to the preparation of the most frequently used PET-tracer 2-[^{18}F]-fluoro-2-desoxy-D-glucose in large amounts [18]. This radiopharmaceutical is now extensively used in neurology, cardiology and oncology. It is estimated that worldwide a few million patients per year are treated using this radiopharmaceutical. Today, the whole PET technology (consisting of cyclotron, radionuclide production unit, and automated radiosynthesis apparatus) is commercially available. It is now reaching almost all corners of the globe.

2.4 Radionuclides for internal radiotherapy

As mentioned above, for internal radiotherapy β^-, α-, Auger electron and X-ray emitters are of great interest [*cf*. 1, 19]. In the simplest case the radiation emitter is brought mechanically to the vicinity of the tumour to be treated. This type of therapy, known as brachytherapy, is commonly performed with ^{192}Ir ($T_{1/2} = 73.8$ d) in the form of a wire, ^{125}I ($T_{1/2} = 59.4$ d) as a stent or ^{103}Pd ($T_{1/2} = 17.0$ d) as a seed or a stent. In the case of ^{192}Ir, the long-range β^- particles are effective but in the latter two cases, X-rays cause the therapeutic effect. After a given period the radioactive source is removed from the organ. A more common application is palliative therapy. Radionuclides like ^{32}P ($T_{1/2} = 14.3$ d) and ^{90}Y ($T_{1/2} = 2.7$ d), which are pure β^- emitters with rather high β^- energy, are introduced into joints and cavities as gels, glass microspheres or conglomerates. In case of small joints, ^{169}Er ($T_{1/2} = 9.4$ d) with low β^- energy, is also used. Great care needs to be taken of the size of the particulate matter so that it does not ooze out of the cavity. The interaction of the radiation with the membrane covering the inner surface of the bone leads to palliative effect. A third variation of internal radiotherapy with β^- emitters involves the radiosynthesis of tumour seeking agents. For this purpose the radionuclides ^{89}Sr ($T_{1/2} = 50.5$ d), ^{153}Sm ($T_{1/2} = 1.9$ d), ^{177}Lu ($T_{1/2} = 6.7$ d), ^{188}Re ($T_{1/2} = 17.0$ h) and ^{131}I ($T_{1/2} = 8.0$ d) are commonly used, the first four in case of bone metastases and the radionuclide ^{131}I in the form of iodide for treatment of thyroid tumours. Some other radionuclides in development are discussed separately.

Regarding the α-emitters, to date many preclinical and some clinical studies have been performed using ^{211}At ($T_{1/2} = 7.2$ h). In fact the application of ^{211}At has a very long story, but it is still in the research phase. The radionuclide ^{225}Ac is potentially very important but it is still under development and is therefore treated in the next section. As far as Auger electron therapy is concerned, to date most of the experimental studies have been performed using ^{125}I. The low range of the Auger electrons demands that the radiopharmaceutical, *e.g.* a labelled DNA compound, has the chance of reaching the cell nucleus in order to destroy the tumour. Thus ^{125}I finds great interest not only for *in vitro* applications (see above) but is attractive for internal radiotherapy of tumours as well.

The production of the therapeutic radionuclides ^{32}P and ^{89}Sr with high specific activity is carried out in a nuclear reactor *via* the $^{32}S(n, p)^{32}P$ and $^{89}Y(n, p)^{89}Sr$ reactions, respectively. The cross sections are rather low and therefore the yields are also low. Large amounts of ^{89}Sr, for example, are produced at the high fast flux reactor RIAR in Dimitrovgrad, Russia, based on long irradiations of about 60 days [*cf*. 6]. The radionuclide ^{131}I is typically produced *via* the fission process, but the precursor system $^{130}Te(n, \gamma)^{131m,g}Te \rightarrow {}^{131}I$, similar to the $^{124}Xe(n, \gamma)^{125}Xe \rightarrow {}^{125}I$ system described above for ^{125}I, is also used. Both those radionuclides are thus obtained with high specific activity. For the production of the radionuclides ^{90}Y and ^{188}Re, generator systems are used, *viz.* $^{90}Sr/^{90}Y$ and $^{188}W/^{188}Re$. The parent radionuclide ^{90}Sr is separated from fission products, but the parent ^{188}W is produced by double neutron capture on ^{186}W in a high flux reactor, *e.g.* at Oak Ridge or Missouri, USA. Both the parents are long-lived and so special care is needed to assure that the daughter therapeutic radionuclides are isolated free of the parents. As expected, the specific activity of the two products is high, approaching almost theoretically maximum levels.

Regarding ^{177}Lu it should be pointed out that, besides the 6.71 d ^{177}Lu, there exists a longer lived isomeric state ^{177m}Lu ($T_{1/2} = 160$ d) which is undesirable. The direct production *via* the $^{176}Lu(n, \gamma)$-reaction leads to a mixture of both the isomers and since the abundance of the target isotope ^{176}Lu in ^{nat}Lu is only 2.59%, despite the high capture cross sec-

tion of 1780 b, the specific activity of the product ^{177}Lu achieved is not high. In comparison, the indirect production route ^{176}Yb$(n,\gamma)^{177}$Yb $\rightarrow$ ^{177}Lu not only gives ^{177}Lu in no-carrier-added form but also the contamination from ^{177m}Lu is much lower [*cf*. 20]. The emphasis in recent years has been on improvement of chemical separations [*cf*. 3].

In contrast to the above mentioned seven therapeutic radionuclides (*i.e.* ^{32}P, ^{89}Sr, ^{90}Y, ^{125}I, ^{131}I, ^{177}Lu and ^{188}Re) which are produced with high specific activity *via* irradiations in a nuclear reactor, the yield and the specific activity of the radionuclide ^{103}Pd, originally produced in a nuclear reactor *via* the reaction ^{102}Pd$(n,\gamma)^{103}$Pd, could not be improved. The production has therefore shifted from reactor to cyclotron. It is now routinely produced *via* the ^{103}Rh(p,n)-reaction, though the ^{103}Rh$(d,2n)$-process is also interesting (for a recent review on nuclear data *cf*. [21]). Over the last 15 years about 20 cyclotrons have been installed in USA to produce exclusively ^{103}Pd, because this radionuclide is commonly used in treatment of prostate cancer, though now with a declining trend.

As far as the radionuclide ^{153}Sm is concerned, production is done at a reactor *via* the ^{152}Sm(n,γ)-reaction. Consequently the specific activity is not high. On the other hand, since the cross section for this reaction is relatively high (206 b), the specific activity of ^{153}Sm is not as low as in the case of many other radionuclides produced *via* the (n,γ)-reaction.

Regarding the production of the α-emitting radionuclide ^{211}At, the only reaction utilized so far is the ^{209}Bi$(\alpha,2n)^{211}$At process. A precise control of the energy range is absolutely necessary to avoid the formation of the radioisotope ^{210}At which decays to long-lived ^{210}Po ($T_{1/2} = 138.4$ d). The methods of chemical separation of radioastatine from the bismuth target have been well worked out [*cf*. 22]. Other α-emitting radionuclides, presently in development, are discussed below.

3. New developments

In recent years, development work related to radionuclide production has been carried out mainly in four directions:

- Development of novel positron emitters,
- Development of novel highly ionising radiation emitters for internal radiotherapy,
- Development of novel methodologies for production of some established radionuclides,
- Standardisation of production data.

A brief discussion of those areas is given below.

3.1 Novel positron emitters

With the growing significance of PET in diagnostic nuclear medicine, the need for novel positron emitters, also termed as non-standard or innovative positron emitters, has been increasing, especially for studying slower metabolic processes and for quantification of targeted therapy [*cf*. 23, 24]. Those radionuclides, like the commonly used positron emitters, are also produced exclusively at cyclotrons (or accelerators). The subject has been treated in detail in a recent review [25]. In this article, therefore, only some salient features are discussed.

Table 2. Some novel positron emitters for medical applications.[a]

Radionuclide ($T_{1/2}$)	Major production route	Energy range [MeV]	Application[b]
^{38}K (7.6 min)	^{35}Cl(α,n)	22 → 10	Cardiology
^{55}Co (17.6 h)	^{58}Ni(p,α)	15 → 7	Tumour imaging;
	^{54}Fe(d,n)	10 → 5	neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 → 9	Radioimmunotherapy
^{66}Ga (9.4 h)	^{66}Zn(p,n)	13 → 8	Quantification of SPECT-pharmaceuticals
^{72}As (26.0 h)	^{nat}Ge(p,xn)	18 → 8	Tumour imaging; immuno-PET
^{73}Se (7.1 h)	^{75}As$(p,3n)$	40 → 30	Selenopharmaceuticals
^{76}Br (16.0 h)	^{76}Se(p,n)	15 → 8	Radioimmunotherapy
^{86}Y (14.7 h)	^{86}Sr(p,n)	14 → 10	Therapy planning
^{89}Zr (78.4 h)	^{89}Y(p,n)	14 → 10	Immuno-PET
^{94m}Tc (52 min)	^{94}Mo(p,n)	13 → 8	Quantification of SPECT-pharmaceuticals
^{120}I (1.3 h)	^{120}Te(p,n)	13.5 → 12	Iodopharmaceuticals
^{124}I (4.18 d)	^{124}Te(p,n)	12 → 8	Tumour targeting; dosimetry

a: Produced using a small or medium-sized cyclotron.
b: Each application involves PET imaging.

Most of the novel positron emitters have been developed at laboratories where facilities for the production of standard positron emitters already existed. Some of the very promising non-standard positron emitters are given in Table 2. The common route of production of each radionuclide is the low-energy (p,n)-reaction on an enriched target isotope. In a few cases other low-energy reactions, such as (d,n) and (p,α), have also been employed. For all those radionuclides some sort of novel medical application has been reported. For a few radionuclides, like ^{64}Cu, ^{124}I and ^{86}Y, a large number of applications have already been demonstrated. The number of relevant reactions studied has therefore also been correspondingly large [*cf*. 26, 27]. However, the low-energy (p,n)-reaction on an enriched target isotope is favoured because it generally leads to a high-purity product.

A typical excitation function of the commonly used (p,n)-reaction for the production of a novel positron emitter in the medium mass range is shown in Fig. 1. The threshold lies at about 3 MeV and the maximum at about 10 MeV. Thereafter the cross section decreases due to the onset of the competing $(p,2n)$-reaction. The optimum energy range for production is thus between 7 and 14 MeV. This energy region is within the capacity of a small medical cyclotron and therefore (as mentioned above) most of the development work on novel positron emitters has been done at established PET centres. The (p,n)-reaction can be described relatively well by nuclear model calculations and thus, if many data points are available, a theory-based evaluation is possible [28]. Fig. 1 shows, as an example, the data for the excitation function of the ^{64}Ni$(p,n)^{64}$Cu reaction (for original references *cf*. [28]).

The production of the three more widely used novel positron emitters, *viz.* ^{64}Cu, ^{124}I and ^{86}Y, mainly developed at the Research Centre Jülich, is described in some detail below.

The radionuclide ^{64}Cu emits low-energy positrons, has no disturbing γ-ray, has a suitable half-life and forms in-

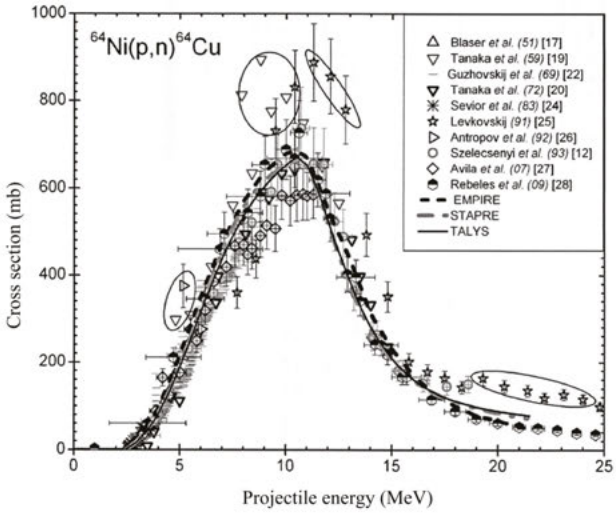

Fig. 1. Experimental data along with the results of nuclear model calculations using the codes EMPIRE, STAPRE and TALYS for the ^{64}Ni$(p, n)^{64}$Cu reaction. The encircled data were deselected in further evaluation (taken from Ref. [28]).

teresting stable co-ordination compounds. It is thus very suitable for studying slow metabolic processes. However, the positron branching is only 17.8% [29], so that much higher radioactivity has to be injected to achieve a coincidence rate similar to that, for example, with ^{18}F-radiopharmaceuticals. In addition, the remaining 82.2% decay branching (β^-, EC) induces a non-negligible radiation dose. Due to this reason ^{64}Cu allows a combination of PET with radioimmunotherapy.

The suggested production route ^{64}Ni$(p, n)^{64}$Cu [30] involves the use of the rather expensive highly enriched target material electroplated on a gold surface. Nonetheless, the technology has been well developed [30–35] for production of ^{64}Cu in batches of about 40 GBq and recovery of the enriched target material. The separation of ^{64}Cu is generally done *via* anion-exchange chromatography. A recent work [36] describes sophisticated targetry calculations. Due to increasing demand for this radionuclide in radioimmunotherapy, presently a commercialization of this production process is being pursued. However, systematic human use is pending.

In comparison to the ^{64}Ni$(p, n)^{64}$Cu reaction, for the ^{64}Ni$(d, 2n)^{64}$Cu reaction only cross section measurements have been reported. Although the expected yield of ^{64}Cu *via* the latter reaction is higher, the availability of only low-energy deuterons at medical cyclotrons has precluded the use of this reaction for production purposes. On the other hand, small amounts of ^{64}Cu have been produced using a deuteron induced reaction on ^{64}Zn [*cf*. 37, 38] as well as *via* an intermediate energy proton induced reaction on enriched ^{68}Zn [*cf*. 39].

The radionuclide ^{124}I is somewhat longer lived ($T_{1/2} =$ 4.18 d) and it has also a relatively low positron branching of 22.0% [*cf*. 29]. The radiation dose from this radionuclide is therefore also higher as compared to standard PET radionuclides. The production route ^{124}Te$(p, n)^{124}$I [*cf*. 40] commonly involves irradiation of a $^{124}TeO_2$ target and removal of radioiodine by a distillation process, whereby the irradiated enriched target is regenerated for reuse [*cf*. 41–45]. The use of a ^{124}Te-metal target followed by a wet chemical separation of radioiodine has not been very successful. The yield of ^{124}I *via* the ^{124}Te(p, n)-reaction is rather low and the product is somewhat expensive but it is of very high radionuclidic purity [*cf*. 27]. Due to increasing demands for this radionuclide, intensified efforts are underway to produce it in larger quantities.

The production of the radionuclide ^{86}Y is carried out *via* the ^{86}Sr(p, n)-reaction [46] on an enriched $^{86}SrCO_3$ target. The five major separation methods for ^{86}Y involve: (a) coprecipitation with $La(OH)_3$ followed by ion-exchange separation of radioyttrium from bulk lanthanum [47, 48], (b) electrolysis [49–51], (c) multiple column chromatography [52], (d) solvent extraction [53] and (e) simple precipitation of the target element [54, 55]. Out of those processes, the electrolytic method appears to be more promising. The radionuclide ^{86}Y has become the most suitable positron emitter for quantification of radiation dosimetry of ^{90}Y-labelled therapeuticals. Due to the ever increasing demand for this radionuclide, its large scale production is either already established or is being planned at several centres.

Despite the above discussed capability of low-energy nuclear reactions on enriched target isotopes to produce many novel positron emitters, there are some radionuclides which can be obtained only using intermediate energy reactions (for a detailed discussion *cf*. [25]). In particular the production of ^{52}Fe ($T_{1/2} = 8.3$ h), ^{73}Se ($T_{1/2} = 7.1$ h), ^{77}Kr ($T_{1/2} = 1.2$ h) and ^{83}Sr ($T_{1/2} = 32.4$ h) by the nuclear reactions ^{55}Mn$(p, 4n)^{52}$Fe, ^{75}As$(p, 3n)^{73}$Se, ^{79}Br$(p, 3n)^{77}$Kr and ^{85}Rb$(p, 3n)^{83}$Sr demands a high intensity cyclotron, acceler-

ating protons of energies up to about 70 MeV (in the case of ^{52}Fe preferably up to 100 MeV).

Although in the intermediate energy range mostly protons are available and are also predominantly used, other charged particles like deuterons, ^{3}He- and α-particles may also induce a few useful reactions. For example, intermediate energy deuterons could be useful in the production of ^{64}Cu *via* the ^{nat}Zn(d,x)-process, a ^{3}He-particle beam in the production of ^{75}Br by the ^{75}As(^{3}He, $3n$)-process and an α-particle beam in the production of ^{38}K and ^{73}Se *via* the ^{35}Cl(α, n)^{38}K and ^{70}Ge(α, n)^{73}Se reactions, respectively (for more details *cf*. [25]).

Similar to some commonly used positron emitters made available *via* generator systems, a few novel and potentially useful positron emitters could also be produced through generators. Some of them are: ^{44}Ti (60.4 a)/^{44}Sc (3.9 h), ^{52}Fe (9.1 h)/$^{52\,m}$Mn (21 min), ^{62}Zn (9.1 h)/^{62}Cu (9.7 min), ^{72}Se (8.5 d)/^{72}As (26.0 h), ^{122}Xe (20.1 h)/^{122}I (3.6 min) and ^{140}Nd (3.4 d)/^{140}Pr (3.4 min). The systems ^{52}Fe/^{52m}Mn, ^{62}Zn/^{62}Cu and ^{122}Xe/^{122}I were proposed rather long time ago (for more details *cf*. [25]). Out of those, more detailed studies have been carried out only on the system ^{62}Zn/^{62}Cu. In general not much progress has been reported regarding their further applications. The systems ^{72}Se/^{72}As [*cf*. 56, 57] and ^{140}Nd/^{140}Pr [*cf*. 58] have great potential and deserve more detailed investigations. The generator system ^{44}Ti/^{44}Sc may also prove to be useful [*cf*. 59, 60], though the parent half-life is very long and the cross section of the ^{45}Sc(p, $2n$)^{44}Ti reaction is rather low [*cf*. 61]. All of the above mentioned parent radionuclides can be produced only using intermediate energy cyclotrons.

3.2 Novel therapeutic radionuclides

3.2.1 General remarks

The number of potentially interesting therapeutic radionuclides is very large, especially among the lanthanoids [*cf*. 62]. However, as mentioned above, in internal radionuclide therapy the emphasis has shifted to low-range but highly ionising radiation emitters. They include low-energy β^- emitters and α-particle emitters as well as Auger and conversion electron emitters. Among the β^- emitters, the radionuclides ^{47}Sc ($T_{1/2} = 3.35$ d; $E_{\beta^-} = 610$ keV), ^{67}Cu ($T_{1/2} = 2.58$ d; $E_{\beta^-} = 577$ keV), ^{105}Rh ($T_{1/2} = 1.47$ d; $E_{\beta^-} = 560$ keV), ^{161}Tb ($T_{1/2} = 6.90$ d; $E_{\beta^-} = 590$ keV), ^{175}Yb ($T_{1/2} = 4.19$ d; $E_{\beta^-} = 466$ keV) and ^{186}Re ($T_{1/2} = 3.72$ d; $E_{\beta^-} = 1070$ keV) have been receiving enhanced attention. Attached to an ideal chemical compound, the therapeutic radionuclide would selectively reach the tumorous cells and cause the therapeutic effect without causing much damage to the healthy surrounding tissue. Some of those radionuclides have been under consideration for a long time, but their production methods have been improving only in recent years, resulting in enhanced interest in novel applications of those radionuclides. A few other β^- emitting radiolanthanides, for example ^{149}Pm ($T_{1/2} = 2.21$ d; $E_{\beta^-} = 1060$ keV) and ^{166}Ho ($T_{1/2} = 1.12$ d; $E_{\beta^-} = 1860$ keV) are also of potential interest for preparing tumour seeking agents.

Concerning targeted α-particle therapy, presently there is great interest in ^{225}Ac ($T_{1/2} = 10.0$ d; $E_{\alpha} = 5830$ keV) which is useful in itself as well as for providing ^{213}Bi ($T_{1/2} = 46$ min; $E_{\alpha} = 5900$ keV) through a generator system. In recent years some interest has also developed in ^{226}Th ($T_{1/2} = 31$ min; $E_{\alpha} = 6340$ keV) which can be obtained through a generator column loaded with ^{230}U ($T_{1/2} = 20.8$ d; $E_{\alpha} = 5890$ keV). A few other potentially useful α-emitters are ^{149}Tb ($T_{1/2} = 4.1$ h; $E_{\alpha} = 3970$ keV), ^{223}Ra ($T_{1/2} = 11.43$ d; $E_{\alpha} = 5720$ keV) and ^{224}Ra ($T_{1/2} = 3.66$ d; $E_{\alpha} = 5683$ keV).

As far as novel Auger electron, conversion electron and X-ray emitters are concerned, it should be mentioned that the radionuclides ^{67}Ga ($T_{1/2} = 3.26$ d) and ^{111}In ($T_{1/2} = 2.8$ d), previously used as SPECT radionuclides, are now also being considered for application in Auger therapy. Other potentially interesting radionuclides are ^{117m}Sn ($T_{1/2} = 13.6$ d, conversion electrons), ^{131}Cs (($T_{1/2} = 9.7$ d; X-rays), ^{140}Nd ($T_{1/2} = 3.37$ d; Auger electrons), ^{193m}Pt ($T_{1/2} = 4.33$ d; Auger electrons) and ^{195m}Pt ($T_{1/2} = 4.02$ d; Auger electrons).

3.2.2 Novel low-energy β^- emitters

The production of the six low-energy β^- emitting radionuclides mentioned above, *viz*. ^{47}Sc, ^{67}Cu, ^{105}Rh, ^{161}Tb, ^{175}Yb and ^{186}Re, was started using a nuclear reactor, and in the case of ^{47}Sc, ^{105}Rh and ^{161}Tb it is still done at reactors, although following modified routes to achieve higher specific activity. The radionuclide ^{47}Sc is produced either *via* the ^{46}Ca(n, γ)^{47}Ca $\xrightarrow{\beta^-}$ ^{47}Sc process or through the ^{47}Ti(n, p)^{47}Sc reaction. In both cases a highly enriched target is needed. The production *via* the ^{47}Ti(n, p)^{47}Sc reaction is more economical and the radionuclide has been produced in quantities sufficient for applications, though only using the high flux reactor at BNL [*cf*. 63, 64]. For the production of ^{105}Rh, the process ^{104}Ru(n, γ)^{105}Ru $\xrightarrow{\beta^-}$ ^{105}Rh is utilized [*cf*. 65]. The radionuclide ^{161}Tb is produced through the process ^{160}Gd(n, γ)^{161}Gd $\xrightarrow{\beta^-}$ ^{161}Tb [*cf*. 62]. In the case of ^{175}Yb, production is still done using the ^{174}Yb(n, γ)-reaction, since the possible route ^{175}Lu(n, p)^{175}Yb, expected to give a higher specific activity product, has so far not been developed.

In contrast to ^{47}Sc, ^{105}Rh, ^{161}Tb and ^{175}Yb, the production of the radionuclides ^{67}Cu and ^{186}Re is shifting over to cyclotrons. The quality and quantity of ^{67}Cu produced by the ^{67}Zn(n, p)^{67}Cu reaction in a nuclear reactor do not meet the specifications required for its use in radioimmunotherapy due to many active and inactive impurities. Its production has been investigated at a small cyclotron ($E_p = 18 \rightarrow 12$ MeV) through the reaction ^{70}Zn(p, α)^{67}Cu on an enriched target [*cf*. 66]. The yield is, however, low. More promising is the ^{68}Zn(p, $2p$)^{67}Cu reaction using high-energy protons. This route was applied earlier [*cf*. 67, 68]. However, since ^{nat}Zn was used as target material, the specific activity achieved was rather low for radioimmunotherapeutic applications due to the formation of stable ^{63,65}Cu [*cf*. 64]. Some recent radiochemical measurements [*cf*. 69] show that a highly enriched ^{68}Zn target and the energy range $E_p = 70 \rightarrow 30$ MeV lead to ^{67}Cu of high quality. A comparison of the ^{67}Cu yields calculated from the excitation functions of the two production reactions developed at cyclotrons, namely ^{70}Zn(p, α)^{67}Cu and ^{68}Zn(p, $2p$)^{67}Cu, is given in Fig. 2. Evidently the latter reaction is more suitable,

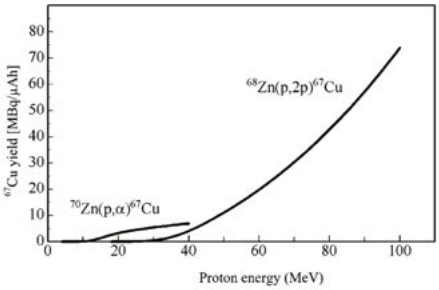

Fig. 2. Integral yields of ^{67}Cu in proton-induced production reactions on highly enriched target isotopes ^{68}Zn and ^{70}Zn, shown as a function of proton energy (curves are based on the numerical values given in Ref. [117]).

but it demands an intermediate energy cyclotron. In view of the great therapeutic potential of this radionuclide, considerable efforts are underway in several laboratories to produce it efficiently, mainly *via* the ^{68}Zn$(p, 2p)^{67}$Cu process, *i.e.* using about 70 MeV protons.

Very recently the reaction ^{70}Zn$(d, \alpha n)^{67}$Cu on highly enriched ^{70}Zn has also been investigated over the deuteron energy range of 10 to 20 MeV [70]. The reaction cross sections and the ^{67}Cu yield are about 50% higher than those for the ^{70}Zn$(p, \alpha)^{67}$Cu reaction. However, the rare availability of high-intensity 20 MeV deuteron beam and the high cost of the enriched target material may be restrictive factors in the use of this reaction for production purposes.

With regard to the production of ^{186}Re, the original ^{185}Re$(n, \gamma)^{186}$Re reaction has been dropped due to the resulting low specific activity. The new method of preparation of this radionuclide is the ^{186}W$(p, n)^{186}$Re reaction, though the ^{186}W$(d, 2n)^{186}$Re reaction has also been investigated and gives higher yield than the (p, n) reaction. Most of the studies deal with nuclear reaction cross-section measurements [for a review *cf*. 71]. Only in three works [72–74] small scale production has also been reported. A recent critical analysis [71] showed that, for obtaining a high-purity product, an enriched ^{186}W target is absolutely necessary and the maximum proton energy used should not exceed 18 MeV. The formation of the very long-lived isomer, ^{186m}Re ($T_{1/2} = 2 \times 10^5$ a) also needs special consideration in both (p, n) and $(d, 2n)$ reactions. Presently, efforts are underway in a few laboratories to produce this radionuclide in larger quantities, without which its availability will remain limited.

Research and development work on the production of many other potentially useful β^- emitting radionuclides, especially lanthanoids, is also going on. This involves mainly nuclear reaction cross-section measurements using charged particles and development of chemical separations for reactor neutron irradiated targets.

3.2.3 Novel α-emitters

Extensive effort is presently being invested in the development of ^{225}Ac. On one hand its separation from nuclear waste (^{229}Th) is being optimised and, on the other, the ^{226}Ra$(p, 2n)^{225}$Ac reaction, making use of the radioactive target material ^{226}Ra, is being developed [*cf*. 75]. A third possibility under investigation is its production *via* irradiation of ^{232}Th with intermediate energy protons [76, 77]. In the latter case, however, strong chemical effort is involved to separate the desired radionuclide from the fission products.

The α-emitting radionuclide ^{223}Ra holds great promise for bone cancer therapy [78]. It was obtained via the chain ^{226}Ra$(n, \gamma)^{227}$Ra (42.2 min) $\xrightarrow{\beta^-}$ ^{227}Ac (21.77 a) $\xrightarrow{\beta^-}$ ^{223}Ra. Another potentially interesting production route entails the irradiation of ^{232}Th with intermediate energy protons [*cf*. 76].

The production of ^{230}U (and its daughter ^{226}Th) has been studied by ^{231}Pa$(p, 2n)^{230}$U, ^{231}Pa$(d, 3n)^{230}$U and ^{232}Th$(p, 3n)^{230}$Pa $\xrightarrow{\beta^-}$ ^{230}U processes [79–81]. The target material ^{231}Pa is radioactive; the chemical separation involved is thus very demanding [79]. There appears to be some potential for therapeutic application of this radionuclide.

The radionuclide ^{149}Tb is a rather exotic but an interesting α-emitter, particularly because of its low α-particle energy of about 4 MeV. It has been produced to date by two high-energy processes, namely ^{nat}Gd$(p, xn)^{149}$Tb (at $E_p >$ 100 MeV) and ^{165}Ho$(p, \text{spall})^{149}$Tb (at $E_p > 200$ MeV), as well as by the heavy-ion induced reaction ^{141}Pr$(^{12}$C$, 4n)^{149}$Tb. Further development work will depend on the demonstrated therapeutic utility of this radionuclide.

3.2.4 Novel Auger electron emitters

The production of the radionuclides ^{67}Ga and ^{111}In, used previously for SPECT studies and now being considered for Auger electron therapy, is well established (see above). In both cases the $(p, 2n)$-reaction on an enriched target is used [*cf*. 4]. The same is true for ^{77}Br ($T_{1/2} = 57.0$ h). It was previously regarded as a SPECT nuclide but is now being considered more for Auger therapy. Regarding the potentially interesting Auger electron emitters ^{131}Cs, ^{140}Nd, ^{165}Er, ^{169}Yb, ^{193m}Pt and ^{195m}Pt, various production methods are under investigation. The radionuclides ^{165}Er and ^{169}Yb are produced by the (n, γ)-reaction which again results in low specific activity. Several charged particle induced reactions have been investigated for their production in no-carrier-added form. However, both the radionuclides appear to be unsuitable for open source therapy: the half-life of ^{165}Er is too short and that of ^{169}Yb rather long. ^{169}Yb is being considered for brachytherapy, possibly as a substitute for ^{192}Ir. But for that purpose the reactor production of ^{169}Yb appears to be adequate. The radionuclide ^{131}Cs, on the other hand, is of considerable promise for prostate cancer brachytherapy and it may compete with the well-established radionuclide ^{103}Pd mentioned above. Its effective production through the ^{131}Xe$(p, n)^{131}$Cs reaction has been demonstrated [*cf*. 82]. The radionuclide ^{140}Nd is interesting, not only because of its therapeutic effect but also because of its positron-emitting short-lived daughter nuclide ^{140}Pr which allows its localisation *via* PET imaging. Its production is carried out either by the ^{nat}Ce$(^3$He$, xn)^{140}$Nd process or through the ^{141}Pr$(p, 2n)^{140}$Nd reaction [*cf*. 83].

The radionuclides ^{193m}Pt and ^{195m}Pt are pure X-ray and Auger electron emitters, each decay leading to more than

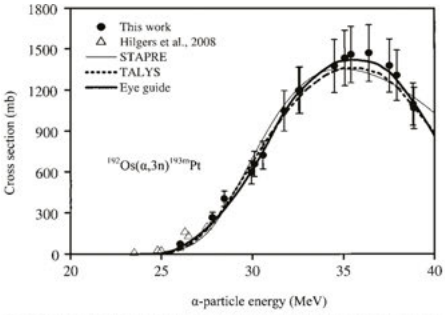

Fig. 3. Experimentally determined and theoretically calculated cross section data for the ^{192}Os$(\alpha, 3n)^{193m}$Pt reaction, shown as a function of the α-particle energy. The model calculations were done using the codes TALYS and STAPRE (taken from Ref. [85]).

30 secondary electrons. Furthermore, platinum-complexes (like cis-di-chlorodiaminplatinum) have been in use in chemotherapy as potent antitumour agents for a long time. Thus both those radionuclides have great potential in Auger electron therapy. So far the major drawback in their widespread use has been their non-availability with a high specific activity. In a recent study it could be shown that small amounts of ^{195m}Pt could be produced with high specific activity *via* the ^{192}Os$(\alpha, n)^{195m}$Pt reaction [84]. Using the same target but higher energy α-particles, on the other hand, it was found that ^{193m}Pt of high specific activity could be advantageously produced through the ^{192}Os$(\alpha, 3n)^{193m}$Pt reaction [85]. The excitation function of this reaction is shown in Fig. 3. It is reproduced very well by nuclear model calculations. Over the optimum energy range $E_\alpha = 40 \rightarrow 30$ MeV, ^{193m}Pt theoretical yield amounts to about 10 MBq/μA h. Thus this radionuclide can be produced in quantities sufficient for therapeutic applications. This has already been practically demonstrated [86].

3.3 Novel methodologies for production of some established radionuclides

There may be several motivations behind the search for novel methodologies for production of some established radionuclides, *e.g.*, to

- increase the yield, radionuclidic purity or specific activity of the desired product,
- produce the daughter nuclide directly, if the parent of a generator system is not easily available,
- achieve more security in the supply of the radionuclide due to technical constraints regarding irradiation facility.

The first motivation has been amply discussed above. The shifts in the production of ^{64}Cu, ^{67}Cu, ^{103}Pd, ^{186}Re and ^{193m}Pt from reactor to cyclotron serve here as very good examples. Charged-particle induced reactions generally give products of higher specific activity. In some cases, however, even an alternative route does not serve the purpose. For production of ^{153}Sm, ^{159}Gd, ^{169}Er, ^{192}Ir and several other radionuclides in the group of lanthanoids, for example, extensive charged-particle induced reaction cross-section measurements have been performed at Brussels, Debrecen and Jülich, but no suitable alternative route has been found to replace the (n, γ)-reaction and thus increase the specific activity of the desired product. Only in the case of ^{153}Sm, the ^{150}Nd(α, n)-reaction on a highly enriched target bears some promise [*cf*. 87] to provide a high specific activity product. The cost would, however, be rather high.

In recent years considerable methodological development has followed also on some known generators to improve their performance (*e.g.* minimisation of breakthrough, improvement in elution yield, concentration of the eluate, *etc.*). Of particular interest in this respect is the ^{68}Ge/^{68}Ga system where extensive work has led to a very efficient processing of the ^{68}Ga-eluate for medical application [*cf*. 88, 89]. In view of the increasing importance of ^{68}Ga in labelling molecules for PET studies [*cf*. 90–93] this methodology holds great promise.

Under the second motivation, attempts related to "in-house" direct production of two generator products, namely ^{62}Cu ($T_{1/2} = 10$ min) and ^{68}Ga ($T_{1/2} = 1.13$ h), may be mentioned. The ^{62}Zn/^{62}Cu generator demands frequent production of the parent ^{62}Zn at a 30 MeV cyclotron because it is rather short-lived ($T_{1/2} = 9.13$ h). It was therefore thought worthwhile to produce ^{62}Cu directly through the ^{62}Ni(p, n)-reaction on an enriched target at a small-sized cyclotron [94] or *via* the ^{59}Co(α, n)-reaction on a natural target at a medium-sized cyclotron [95]. Those procedures have, however, not found much practical application because of the short half-life of ^{62}Cu. Regarding the second system, *viz.* ^{68}Ge/^{68}Ga generator, though commercially developed, the availability is rather limited. In view of the ever enhancing importance of ^{68}Ga, the notion is developing to produce this radionuclide directly through the ^{68}Zn(p, n)-reaction on an enriched target at a small-sized cyclotron or *via* the ^{65}Cu(α, n)-reaction on ^{nat}Cu at a medium-sized cyclotron (for more discussion *cf*. [96]). The prospects for direct production of this radionuclide appear to be favourable, though the effort involved will be much more than in the generator elution.

The most conspicuous and important example under the third motivation is that of ^{99m}Tc. As discussed above, the supply of this commonly used diagnostic radionuclide is rather jeopardized due to increasing uncertainty in the availability of the fission produced ^{99}Mo for preparing a generator system. An intense search for alternative routes of production of ^{99}Mo and ^{99m}Tc is therefore imminent. This topic is therefore discussed in more detail.

3.3.1 Alternative routes of production of ^{99}Mo and ^{99m}Tc

The suggested routes which are not dependent on a nuclear reactor are given below:

(a) ^{nat}U$(\gamma, f)^{99}$Mo; (b) ^{232}Th$(p, f)^{99}$Mo;
(c) ^{100}Mo$(\gamma, n)^{99}$Mo; (d) ^{100}Mo$(n, 2n)^{99}$Mo;
(e) ^{100}Mo$(p, d + pn)^{99}$Mo; (f) ^{100}Mo$(d, t + p2n)^{99}$Mo;
(g) ^{100}Mo$(p, 2n)^{99m}$Tc; (h) ^{100}Mo$(d, 3n)^{99m}$Tc.

It has been suggested [97] that high-energy photons produced at accelerators could be used for production of ^{99}Mo

via photofission of ^{nat}U. This would lead to high specific activity ^{99}Mo, but due to the low photofission cross section of ^{nat}U (160 mb), the yield of ^{99}Mo would be by a factor of about 3.5×10^3 lower than that in the neutron induced fission of ^{235}U. The yield could be increased by developing a high power accelerator, but this has yet to be demonstrated.

The cross section for the formation of ^{99}Mo in the fission of ^{232}Th with 22 MeV protons is about 34 mb [98]. Recently, Abbas *et al*. [99] performed a feasibility study and showed that with 40 MeV protons about 50 GBq of ^{99}Mo could be produced. This is a potentially useful reaction, provided a high-current accelerator is made available and an effective procedure for the radiochemical separation of ^{99}Mo is worked out. The expected yields, however, suggest that this procedure could meet the regional demands but not international needs.

The cross section of the ^{100}Mo$(\gamma, n)^{99}$Mo reaction is also small (150 mb at the maximum of the peak at 14 MeV) [*cf*. 100]. A study on the ^{100}Mo$(n, 2n)^{99}$Mo process [*cf*. 101] claims that amounts of ^{99}Mo comparable to those produced through the ^{98}Mo$(n, \gamma)^{99}$Mo reaction in a low flux reactor could be obtained, provided a proper accelerator for 14 MeV neutron production (through the d, t reaction) is developed. The technical difficulties to be overcome are enormous; furthermore, the drawbacks of the ^{99}Mo produced with large amount of the inactive carrier will remain (see discussion above). More attention is therefore presently focused on production of ^{99}Mo and ^{99m}Tc using charged-particle induced reactions on ^{100}Mo.

The possibility of production of ^{99}Mo through the ^{100}Mo$(p, d + pn)^{99}$Mo reaction was investigated under an IAEA-sponsored project, utilizing highly enriched ^{100}Mo target [*cf*. 102]; due to low cross section it was found to be unsuitable. Although GBq amounts of ^{99}Mo could be produced using long irradiations of thick targets covering the energy range $E_p = 65 \rightarrow 10$ MeV, the preparation of the generator and, above all, the recovery of the expensive enriched material would pose great technological and handling problems. Furthermore, the product would not be carrier-free. Although subsequent measurements and evaluations [*cf*. 103–106] showed slightly higher cross sections, the basic conclusion given in [102] did not change. The ^{100}Mo$(d, t + p2n)^{99}$Mo reaction has a threshold of about 20 MeV and the cross section is lower than for the proton induced reaction [*cf*. 107–109]. Furthermore, in this case also the problem of carrier will remain. It is therefore concluded that this reaction is also not suitable for routine production of ^{99}Mo, being even less favourable than the ^{100}Mo$(p, d + pn)$ reaction.

It was also concluded that the direct route of production of ^{99m}Tc *via* the ^{100}Mo$(p, 2n)^{99m}$Tc reaction at a cyclotron using 22 MeV protons on the target is worth considering for local production and consumption [102]. The corresponding ^{100}Mo$(d, 3n)^{99m}$Tc reaction with 25 MeV deuterons would give a slightly higher yield of ^{99m}Tc [107–109], but as deuterons of that energy are rarely available with high intensities, the method is presently not of much interest. As regards the ^{100}Mo$(p, 2n)^{99m}$Tc reaction, recently some more accurate cross section measurements have been done [104–106] and its practical application was demonstrated first by Guérin *et al.* [110] and later by Morley *et al.* [111]. The quality of cyclotron-produced ^{99m}Tc with regard to radiopharmaceutical production was found to be similar to that obtained *via* the ^{99}Mo/^{99m}Tc generator system.

However, the effect of the long-lived impurities (^{97g}Tc, ^{98}Tc, ^{99g}Tc; all with $T_{1/2} > 10^5$ a) on the ^{99m}Tc specific activity has still to be investigated [*cf*. 112], as well as the achievable radionuclidic purity as a function of the isotopic composition of the enriched ^{100}Mo target [*cf*. 112, 113]. In fact they may both become the deciding factors in the use of the cyclotron-produced ^{99m}Tc.

A critical analysis of the ^{100}Mo$(p, 2n)^{99m}$Tc route for the production of ^{99m}Tc at a cyclotron suggests that four basic requirements will have to be fulfilled to make this method effective:

1. Use of highly enriched ^{100}Mo target, including efficient recycling,
2. Radiochemical separation immediately after irradiation,
3. Daily production schedule,
4. Good logistics.

The target enrichment is crucial. If it is of low enrichment, several radionuclidic impurities (^{95m}Tc, ^{96m}Tc, *etc*.) will occur as it has been shown in recent studies [*cf*. 112, 113]. The radiochemical separation of ^{99m}Tc from a $^{100}MoO_3$ target could be performed *via* thermochromatography, as it was done in the case of ^{94m}Tc from a $^{94}MoO_3$ target [114]. Alternatively, a wet chemical method using ion-exchange chromatography could be used [*cf*. 110, 115]. An important aspect is also the recovery of the enriched target material. Finally, due to its short half-life, the production of ^{99m}Tc will have to be done on a regular (daily) basis, and the supply of various nearby laboratories would need good logistics.

The on-going development work will certainly lead to sufficient quantities of ^{99m}Tc for local or regional use, provided the level of the ^{99g}Tc impurity is comparable to that in the generator produced ^{99m}Tc. However, this author is convinced that it is illusory to expect that the cyclotron production of ^{99m}Tc will solve the world shortage problem. For large scale production and supply to all parts of the world, the utilization of the ^{235}U(n, f)-process will remain a necessity, though intensive efforts need to be invested to shift the process from high enrichment uranium (HEU) target to low enrichment uranium (LEU) target.

3.4 Standardisation of production data

As described above, presently extensive research and development work on various aspects of production of medical radionuclides is going on in many of laboratories. It is therefore imperative that some sort of evaluation of the reported information is done to standardise the data and procedures to be able to assist the user in production of medical radionuclides of acceptable quality.

As regards commonly used reactor radionuclides, extensive neutron-induced reaction cross section data are available in several evaluated nuclear data files (*e.g.* ENDF/B-VII), thanks to energy-related reactor programmes, and an excellent manual [2] has been prepared concerning other production details of those radionuclides.

For accelerator-based radionuclides, whereas vast information is available, particularly on targetry and chemical

separation procedures, no authentic standardisation work has been reported. The main reason is that each laboratory uses a methodology suitable to its own cyclotron and radiochemistry facility. As regards nuclear data for production, however, the situation is better and is discussed below.

All charged-particle induced reaction cross section data are promptly compiled in the EXFOR file coordinated by the IAEA. For potentially interesting production reactions, generally a large number of measurements are available in the literature. It appeared therefore incumbent to devote some effort to the evaluation of those data. The IAEA embarked on this mission about 15 years ago and organised two successive co-ordinated research programmes (CRPs) in which about a dozen laboratories participated, under guidance of the Research Centre Jülich. Since no evaluation methodology existed for charged-particle induced reactions, the initial work was rather empirical. However, in later years strong application of nuclear models could be built in. The evaluated and recommended data for the major diagnostic radionuclides are now available in [116] and those for the therapeutic radionuclides in [117]. They should allow a proper selection of the projectile energy range in a target to ensure high radionuclidic purity of the desired product. In addition, the exact yields of the desired radionuclide and the accompanying radioactive impurities can be accurately calculated. A few groups are now also individually engaged in this type of work [*cf*. 21, 118].

Further work on the validation of evaluated data as well as on the evaluation of data for other emerging radionuclides is necessary.

4. Future directions and perspectives

Radioactivity has revolutionized medicine. The radionuclide production technology is well developed and several suitable radiopharmaceuticals are now widely available for patient care, both with respect to diagnosis and radiotherapy. The future prospects of the tracer technology look bright. However, innovative notions and approaches will need to be followed to keep pace with other medical imaging diagnostic and therapeutic techniques. The emerging problems will demand enhanced attention in the following directions.

4.1 Patient care programme

With regard to the apprehension about the secure supply of the most commonly used diagnostic radionuclide ^{99m}Tc, presently produced by fission of highly enriched ^{235}U, it is likely that the industry would modify the industrial production process to be able to cope with the use of low-enriched ^{235}U (thereby reducing the danger of nuclear weapons' proliferation). The dependence on nuclear reactors will, however, remain. If at the same time some countries in the OECD-area may decide to utilize a few modern research reactors for production of fission ^{99}Mo, the situation may improve. At least one initiative to make use of the München reactor for this purpose appears promising. Furthermore, if a few new powerful research reactors could be constructed in countries with fast developing economies and technologies, *e.g.* China, the problem could be solved. On the other hand, if no progress is made in the above mentioned three directions, several scenarios may emerge, *e.g.*

1. Cyclotron production of ^{99m}Tc. As mentioned above, the question of short- and long-lived impurities needs urgently to be solved. Furthermore, this would offer only a regional solution in technologically advanced countries. It will be beyond the reach of developing countries.
2. Production of ^{99}Mo by fission of low-enriched ^{235}U for regional (not global) supply. Countries like Argentina, South Africa, Russia, India, Pakistan, Ukraine, *etc.* could do so. Some of them are already developing the methodology and producing appreciable quantities of fission ^{99}Mo.
3. Enhanced production of ^{99}Mo through the (n, γ) reaction and intensified efforts to make use of the gel generator, as it is done today in a few developing countries.
4. Development of future technologies, *e.g.* production of ^{99}Mo by fission of ^{nat}U, using an accelerator based intense photon or spallation neutron source. The spallation neutron source would be very suitable also for the production of several therapeutic radionuclides *via* the (n, p) reaction [*cf*. 119].
5. Enhanced production and application of ^{123}I in SPECT studies.
6. Enhanced application of PET technology using ^{18}F and ^{68}Ga labelled compounds. Large amounts of ^{18}F could possibly be produced by using large-sized $H_2{}^{18}O$ targets and proton energies of up to 30 MeV [*cf*. 120]. For producing large quantities of ^{68}Ge (the parent of ^{68}Ga) *via* the ^{69}Ga$(p, 2n)$-reaction, high-current targetry for gallium irradiation will be required (see discussion under Sect. 2.3). The generator preparation methodology itself has reached sophistication [*cf*. 88, 89].

Thus considerable efforts may be called upon to ensure the smooth running of patient care programmes.

4.2 Research orientations

For research studies, the demand for longer lived positron-emitting radionuclides, which have passed the stage of laboratory scale production and clinical evaluation, *e.g.* ^{64}Cu, ^{86}Y, ^{89}Zr and ^{124}I, will certainly increase. The same may be true for other potentially useful positron emitters, such as ^{55}Co, ^{71}As, ^{72}As and ^{73}Se. If the demands for those radionuclides increase further, it may become incumbent to intensively search for intermediate energy production routes leading to higher yields and purity.

With regard to quantification of SPECT-radiopharmaceuticals, an analogue approach is applied which involves the use of a positron-emitting nuclide of the chemical element of the SPECT radionuclide. Thus for quantification of several ^{99m}Tc-radiopharmaceuticals, labelling of the compound was carried out using the positron emitting radionuclide ^{94m}Tc ($T_{1/2} = 52$ min) followed by a PET measurement. If the shortage of ^{99m}Tc becomes acute, it is likely that ^{123}I-radiopharmaceuticals will play a more important role in the future than today. For quantification of those radiopharmaceuticals, resort may have to be made to a short-lived positron emitting radioiodine, *e.g.* ^{120}I ($T_{1/2} = 1.3$ h).

An important application of positron emitters is in quantification of radiation dose in internal radionuclide therapy.

Combining a positron-emitting isotope of an element together with a therapeutic radioisotope of the same element, it is possible to measure the uptake kinetics by PET imaging, thereby allowing an accurate dosimetric calculation related to therapy. The principle was first applied in the case of internal therapy with ^{90}Y ($T_{1/2}$2.7 d) after mixing it with the positron emitter ^{86}Y ($T_{1/2} = 14.7$ h) [*cf*. 121]. This concept is finding increasing application. A β^- (or Auger electron) and β^+ emitting pair of radionuclides of the same element is now termed as a theragnostic pair [*cf*. 64]. There are several such pairs, *e.g.* ^{89}Sr ($T_{1/2} = 50.0$ d, β^-)/^{83}Sr ($T_{1/2} = 32.2$ h, β^+); ^{131}I ($T_{1/2} = 8.0$ d, β^-)/^{124}I ($T_{1/2} = 4.18$ d, β^+); ^{47}Sc ($T_{1/2} = 3.35$ d, β^-)/^{44}Sc ($T_{1/2} = 3.9$ h, β^+); ^{67}Cu ($T_{1/2} = 2.6$ d, β^-)/^{64}Cu ($T_{1/2} = 12.7$ h, β^+); ^{67}Ga ($T_{1/2} =$ 3.3 d, Auger electrons)/^{68}Ga ($T_{1/2} = 67.6$ min, β^+) and ^{111}In ($T_{1/2} = 2.8$ d, Auger electrons)/^{110g}In ($T_{1/2} = 1.1$ h, β^+). Further development of those pairs would demand considerable efforts which, however, would depend on demonstrated novel applications based on a combination of PET imaging and targeted therapy.

Regarding internal radiotherapy, presently a shift is taking place from the use of β^- particle emitters to Auger electron and α-particle emitters which induce more cellular effects. Several radionuclides are at the development stage (see above, Sect. 3.2), but once the principles have been established, the demands for those radionuclides will increase. Many of them are low-lying, highly converted, high spin states and are difficult to produce. Versatile nuclear routes will have to be harnessed, involving also intermediate energy reactions or even heavy-ion induced reactions. In short, elegant interdisciplinary approaches will be needed to obtain the desired radionuclides in high yield and purity.

A new perspective of medical radionuclides is emerging through extremely significant developments that are currently taking place in organ imaging. The dynamic and quantitative nature of PET (and recently to some extent also SPECT) is being coupled with X-ray tomography (CT) and magnetic resonance imaging (MRI) to provide a highly powerful combination of systems for organ imaging. The radionuclides of potential interest for the latter combination are considered below.

In MRI the elements Mn and Gd are often used as contrast agents. If a positron-emitting radionuclide is introduced in the system, the high-resolution of MRI and the quantitative nature of PET could lead to very high quality imaging. In the case of manganese the positron emitting radionuclide ^{51}Mn ($T_{1/2} = 46.2$ min) has been suggested [*cf*. 122, 123]. Regarding gadolinium, no positron-emitting radionuclide is available. However, it has been demonstrated that this element could be converted to a so-called "intelligent (responsive) agent" [*cf*. 124] by chemically binding it with a metal like Cu through pyridine [125]; This considerably increases the contrast. Now if copper could be a positron emitter, *e.g.* ^{64}Cu, PET and MRI could be advantageously combined. A newer concept involves the conversion of a transition metal complex from the dia- to paramagnetic state (spin crossover) which can be used as a contrast agent [*cf*. 124–127]. The metals of interest are Fe and Ni and the potentially useful positron emitting radionuclides could be ^{52}Fe ($T_{1/2} = 8.3$ h) and ^{57}Ni ($T_{1/2} = 36.0$ h), respectively. In view of the increasing interest in multimode imaging, the need for further development of suitable novel positron emitters will certainly increase.

Another long-term perspective of radionuclide technology could involve an intensive combination of radioactivity and nanotechnology. In recent years, the latter technology has made tremendous progress and its applications are now in many fields, including nuclear energy technology [*cf*. 128]. Also in medical radionuclide research, nanotechnology has found some connection, *e.g.* in production of a radionuclide for nanobioscience application [*cf*. 129], in construction of a generator column using a nanomaterial [*cf*. 130] and in retention of the recoiling daughter in an *in vivo* generator used in alpha radionuclide therapy [*cf*. 131]. Similarly, nanotargeted materials are finding increasing applications in tumour imaging and tumour therapy (for recent reviews *cf*. [132, 133]). The types of needed radionuclides are generally the same as in conventional diagnosis and therapy described above.

5. Concluding remarks

It should be mentioned that also in the future the radionuclide production technology will strongly depend on research reactors as well as small and medium-sized cyclotrons with energies up to about 30 MeV. For production of many emerging radionuclides, however, intermediate-energy, high-intensity accelerators with proton energies up to about 100 MeV will be required. Furthermore, there will be a need for higher energy facilities to accelerate also deuterons, ^{3}He and ^{4}He particles in order to extend the range of production and to improve the radionuclidic purity. In particular the ^{4}He particle beam may be quite advantageous for producing many of the therapeutic radionuclides. Needless to say, that highly qualified personnel with expertise in interdisciplinary areas of physics, chemistry, biology, medicine and engineering will always be needed to maintain, nurture and further develop this sophisticated technology for the benefit of human beings.

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Appendix VII

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New trends in nuclear data research for medical radionuclide production

By S. M. Qaim*

Institut für Neurowissenschaften und Medizin, INM-5: Nuklearchemie, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

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Summary. Nuclear reaction cross section data are of great significance in optimisation of production routes of radionuclides. This article deals with some newer aspects of data research related to production of both standard and novel radionuclides. The recent work to standardise the known data is discussed and new measurements with regard to further optimisation of production routes of some commonly used radionuclides are mentioned. Attempts to increase the specific activity of some reactor-produced radionuclides through the use of charged-particle induced reactions are outlined. The jeopardy in the supply of ^{99m}Tc *via* a fission-produced ^{99}Mo/^{99m}Tc generator is considered and its possible direct production at a cyclotron is briefly discussed. Regarding the novel radionuclides, development work is presently focussed on non-standard positron emitters for diagnosis and on low-range highly ionising radiation emitters for internal radiotherapy. Recent nuclear reaction cross section measurements related to the production of the two types of radionuclides are briefly reviewed and some anticipated trends in nuclear data research are considered.

1. Introduction

Radionuclides find application in both medical diagnosis and internal radiotherapy [*cf*. 1]. A suitable radionuclide in a proper chemical form is generally administered into the human body to allow diagnostic studies or to induce therapeutic effect. The underlying principle of *in vivo* medical diagnosis is that the radiation dose to the patient is minimum. This is achieved through imaging of the human organ from outside of the body using short-lived radionuclides, emitting predominantly a gamma ray in the energy range of 70–250 keV or a positron. The low-energy gamma ray facilitates single photon emission computed tomography (SPECT), and the positron emitter allows positron emission tomography (PET). In contrast to diagnosis, internal radiotherapy stipulates that a certain radiation dose is specifically deposited in the malignant tissue. This is brought about through the use of radionuclides emitting corpuscular radiation, *i.e.*, alpha- or beta-particles, or Auger and conversion electrons, in combination with a targeted-compound labelled with the radionuclide. In all those applications a knowledge of nuclear data plays an important role. Whereas the radioactive decay data are of importance in the choice of a radionuclide for a particular diagnostic or therapeutic application, the nuclear reaction cross section data are of great significance in optimisation of the production route of a desired radionuclide (for earlier reviews [*cf*. 2–7]).

The production of radionuclides is carried out using nuclear reactors as well as cyclotrons. In reactor production generally (n, γ) and (n, f) processes are utilized. Occasionally (n, p) and double neutron capture reactions are also used. The radioactive products are often neutron excess radionuclides. They mostly decay by β^- emission and are therefore especially suited for internal radiotherapy. The cyclotron produced radionuclides, on the other hand, are mainly neutron deficient and decay by electron capture (EC) or β^+ emission. They are therefore ideally suited for diagnostic studies. The positron emitters are almost exclusively produced using charged-particle accelerators. For production of some radionuclides both nuclear reactors and cyclotrons (accelerators) are extensively used.

This article deals with nuclear reaction cross section data for production of medical radionuclides, with emphasis on some newer aspects. The progress made within the last decade is briefly mentioned. It is not the aim of this short review to enlist all recent publications in the field; instead some typical examples for each aspect are given. Some anticipated trends in nuclear data research are outlined.

2. Standardisation of data

A vast amount of experimental data is available in the EXFOR file, coordinated by the IAEA. In the case of neutron-induced reactions, the data have been extensively evaluated and standardised, mainly in the context of energy research, and the recommended data are available in several data files (*cf*. ENDF/B-VII). Those data are useful also for radionuclide production in reactors. Despite this progress,

*E-mail: s.m.qaim@fz-juelich.de.

there was still need of evaluation and standardisation of data for many of the reactor-produced therapeutic radionuclides.

Also for charged-particle induced reactions used in radionuclide production, generally a large number of measurements were available in the literature. However, no serious evaluation effort was reported. The IAEA embarked on this mission about 16 years ago and organised two successive co-ordinated research programmes (CRPs) in which about a dozen laboratories participated. Since no evaluation methodology existed at that time for charged-particle induced reactions, the initial work was rather empirical. It involved normalisation of the data (in case of outdated decay intensities and monitor cross sections), simple nuclear model calculations and statistical fitting of the data. However, in later years strong application of nuclear models could be built in. The evaluated and recommended data for the major diagnostic radionuclides are now available in [8] and those for the therapeutic radionuclides in [9]. The latter includes both reactor and cyclotron produced therapeutic radionuclides. The standardised data should now allow a proper selection of the projectile energy range in a target to ensure high radionuclidic purity of the desired product. In addition, theoretical yields of the desired radionuclide and the accompanying radioactive impurities can be accurately calculated from the evaluated excitation functions. A few groups are now also individually engaged in this type of studies [*cf*. 10, 11]. Further work on the validation of evaluated data as well as on the evaluation of data for other emerging radionuclides is necessary.

3. Optimisation studies relevant to production routes of some standard radionuclides

During the standardisation work it was found that the production data of some commonly used radionuclides were rather discrepant or lacked the required accuracy, calling upon more precise measurements. In a few other cases it was realized that the data for the formation of some impurities needed more attention. A brief account of some newer measurements is given below.

With regard to the standard PET radionuclides, some measurements were done relevant to the production of ^{11}C ($T_{1/2} = 20$ min) *via* the ^{14}N$(p, \alpha)^{11}$C reaction, where the formation of the undesired radionuclides ^{14}O ($T_{1/2} = 70$ s) and ^{13}N ($T_{1/2} = 10$ min) occurs *via* the reactions ^{14}N$(p, n)^{14}$O and ^{14}N$(p, pn)^{13}$N, respectively [12]. The results are shown in Fig. 1. Those data make it possible to calculate the two radioactive impurities formed during the production of ^{11}C. For the optimum proton energy range within the nitrogen gas target ($E_p = 13 \rightarrow 4$ MeV) it is estimated that the ^{11}C formed will contain about 20% ^{14}O and 5% ^{13}N at the end of irradiation. Similarly for the production of ^{18}F ($T_{1/2} = 110$ min) *via* the ^{18}O$(p, n)^{18}$F reaction, the cross section database was extended up to 30 MeV [13], so that large scale production of this radionuclide using medium-sized cyclotrons could be carried out. Furthermore, measurements on the formation of some short-lived positron emitters were extended up to proton energies of about 200 MeV [14]. However, the high-energy data are of more relevance to proton therapy than to radionuclide production.

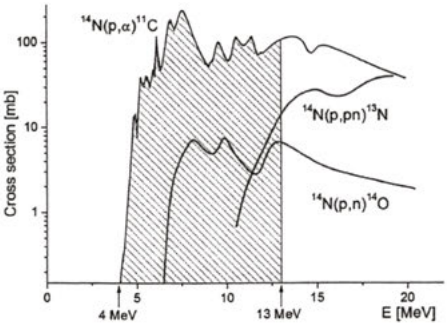

Fig. 1. Excitation functions of proton induced nuclear reactions on ^{14}N (after Ref. [12]).

Some discrepancies existed in the data for the production of the radionuclides ^{68}Ge ($T_{1/2} = 270$ d) and ^{82}Sr ($T_{1/2} = 25.5$ d) which are used as parents of the generator-produced commonly used β^+ emitting radionuclides ^{68}Ga ($T_{1/2} = 1.13$ h) and ^{82}Rb ($T_{1/2} = 1.3$ min), respectively. They are employed especially at PET centres without a cyclotron. A recent measurement on the ^{nat}Rb$(p, x)^{82}$Sr reaction [15] solved the discrepancy about the production data of ^{82}Sr; the measured and calculated thick target yields of ^{82}Sr over different energy ranges were found to be in good agreement [15]. Regarding the production of ^{68}Ge *via* the ^{nat}Ga(p, x)-process, a very recent measurement of the excitation function has strengthened the database [16].

As far as the SPECT radionuclides are concerned, the production data for all five commonly used radionuclides, *viz.* ^{67}Ga ($T_{1/2} = 3.26$ d), ^{99m}Tc ($T_{1/2} = 6.0$ h), ^{111}In ($T_{1/2} = 2.8$ d), ^{123}I ($T_{1/2} = 13.2$ h) and ^{201}Tl ($T_{1/2} = 73.0$ h), are generally well known. Whereas the radionuclide ^{99m}Tc is mostly obtained *via* a fission-produced ^{99}Mo/^{99m}Tc generator system, the other four radionuclides are produced using a medium-sized cyclotron. Only in a few special cases some data problems existed. The production of ^{123}I *via* the ^{124}Xe$(p, x)^{123}$I process, for example, proceeds through two routes, namely ^{124}Xe$(p, 2n)^{123}$Cs $\rightarrow$ ^{123}Xe $\rightarrow$ ^{123}I and ^{124}Xe$(p, pn)^{123}$Xe $\rightarrow$ ^{123}I. Whereas the data for the first route are well established, there exists some discrepancy in the case of direct formation of ^{123}Xe. The effect of the discrepancy on the routine production of ^{123}I is, however, of little significance. The level of the only radionuclidic impurity ^{121}I ($T_{1/2} = 2.1$ h) is negligibly small. However, it has been recently shown [17] that if the incident proton energy exceeds 30 MeV, the cross section of the process ^{124}Xe$(p, x)^{121}$I becomes appreciable. The latter decays to long-lived ^{121}Te ($T_{1/2} = 154$ d) which is a disadvantage. An energy control of the beam incident on the target is therefore mandatory. It has been suggested to limit the beam energy to 35 MeV and reduce the ^{121}Te content by adapting cooling times [17].

For calibration of SPECT machines the long-lived radionuclide ^{57}Co ($T_{1/2} = 271$ d) is commonly used. Some new cross section measurements relevant to its production in no-carrier-added form [18] have strengthened the database.

The status of data for the production of common therapeutic radionuclides is fairly good [*cf*. 9], and only a few new measurements have been performed in recent years. For example, with regard to the production of ^{32}P ($T_{1/2} = 14.3$ d), ^{67}Cu ($T_{1/2} = 2.58$ d) and ^{89}Sr ($T_{1/2} = 50.5$ d) *via* the nuclear reactions ^{32}S(n, p)^{32}P, ^{67}Zn(n, p)^{67}Cu and ^{89}Y(n, p)^{89}Sr, respectively, integral cross section measurements were performed [19, 20] using a 14 MeV d(Be) neutron source. A discussion of the results led to the conclusion that higher yields of those radionuclides would be obtained using a spallation neutron source than the present day fission reactors. Cross section measurements on the production of a few therapeutic radionuclides in a nuclear reactor have also been reported [*cf*. 21, 22].

4. Attempts to improve the specific activity of some reactor-produced therapeutic radionuclides

Many of the therapeutic radionuclides are produced in a nuclear reactor, generally *via* the (n, γ) process, and the specific activity (*i.e.* the radioactivity/unit mass of all isotopes of the element present) achieved is rather low. Some of them can be obtained in no-carrier-added form through precursor decay, generator formation, (n,charged particle) nuclear reaction or fission process. There are, however, several important or potentially important therapeutic radionuclides like ^{103}Pd ($T_{1/2} = 17.0$ d), ^{153}Sm ($T_{1/2} = 1.9$ d), ^{169}Er ($T_{1/2} = 9.4$ d), ^{169}Yb ($T_{1/2} = 32.0$ d), ^{186}Re ($T_{1/2} = 3.7$ d), ^{192}Ir ($T_{1/2} = 73.8$ d), *etc.* where all those methodologies do not function. Furthermore, the production of ^{64}Cu ($T_{1/2} = 12.7$ h) and ^{67}Cu ($T_{1/2} = 2.6$ d) *via* the ^{64}Zn(n, p)^{64}Cu and ^{67}Zn(n, p)^{67}Cu processes does not provide products of sufficient purity. In recent years, therefore, charged-particle induced reactions have been extensively investigated, especially at Brussels, Debrecen and Jülich, to explore the production of those radionuclides in no-carrier-added form. In particular for ^{64}Cu and ^{103}Pd a large number of reactions have been studied [for recent reviews *cf*. 9, 11, 23], out of which the ^{64}Ni(p, n)^{64}Cu and ^{103}Rh(p, n)^{103}Pd processes have been successfully developed for large scale production of the two radionuclides. For ^{67}Cu and ^{186}Re, the methods are still in development (see below). Regarding the other above mentioned radionuclides, the investigated processes [*cf*. 24–30] are not economical because the resulting yields are too low. The radionuclide ^{192}Ir is used in brachytherapy and the radionuclide ^{169}Yb is a potential candidate for brachytherapy. For that purpose the reactor production is adequate. Regarding ^{169}Er, the real application needs to be demonstrated. The main problem regarding the specific activity is thus presently with ^{153}Sm which is now often used in internal radiotherapy. For this radionuclide, the use of the ^{150}Nd(α, n)-reaction on a highly enriched target appears to be of some promise. The measured excitation function [31] is shown in Fig. 2. The yield of ^{153}Sm over the energy range $E_\alpha = 25 \rightarrow 15$ MeV amounts to 2.2 MBq/μA h, with no significant impurity. Thus a high specific-activity and high radionuclidic-purity product could be obtained in a quantity sufficient for medical application, but the cost would be rather high.

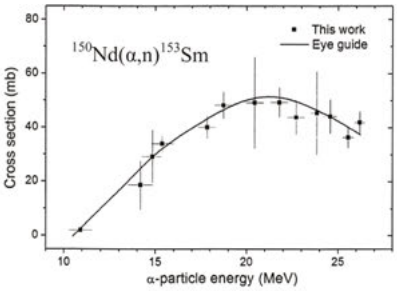

Fig. 2. Excitation function of the ^{150}Nd(α, n)^{153}Sm reaction (after Ref. [31]).

5. Security of supply of ^{99m}Tc and ^{68}Ga: search for alternative production routes

The generator-produced radionuclide ^{99m}Tc ($T_{1/2} = 6.0$ h) is the most commonly used agent in diagnostic studies. Its supply is rather jeopardized due to increasing uncertainty in availability of the fission-produced ^{99}Mo ($T_{1/2} = 66.0$ h) for preparation of generators (ageing reactors, problem with using highly-enriched ^{235}U as target material, *etc.*). An intense search for alternative routes of production of ^{99}Mo and ^{99m}Tc has therefore been going on for more than a decade. Several routes have been suggested and their cross sections have been measured (for a recent review [*cf*. 7]). Out of all those processes the direct production of ^{99m}Tc *via* the ^{100}Mo(p, $2n$)-reaction appears to be more promising. Several measurements have been reported in recent years [32–36] and the data show large scatter, especially over the energy range of 10–20 MeV. Nuclear model calculations show [37] that the more recent data [33–36] are consistent. An evaluation has produced a recommended set of cross sections [37], which should allow calculation of the yield with enhanced confidence. Over the suitable energy range of $E_p = 22 \rightarrow 10$ MeV, the calculated yield of ^{99m}Tc amounts to 700 MBq/μA h. Technical efforts to produce ^{99m}Tc *via* this route are now underway. The levels of long-lived impurities and their implications on the pharmaceutical quality of ^{99m}Tc, however, need to be extensively investigated.

Besides ^{99m}Tc, the availability of the radionuclide ^{68}Ga ($T_{1/2} = 1.1$ h) is also causing some concern. It is a β^+ emitting generator-produced radionuclide and is finding increasing application in PET studies, especially in developing countries. The parent radionuclide ^{68}Ge ($T_{1/2} = 270$ d) is a relatively long-lived cyclotron product and there could be jeopardy about its supply. Some studies on the direct production of ^{68}Ga *via* the ^{68}Zn(p, n)^{68}Ga and ^{65}Cu(α,n)^{68}Ga reactions have been reported [*cf*. 38]. The prospects of direct production of ^{68}Ga are good but, due to low yield, the adopted procedure will remain limited to in-house use.

6. Research-oriented radionuclides

Constant research work is going on with the aim to develop novel radionuclides for newer applications in medicine, both

diagnostic and therapeutic. Many of the nuclear data studies are, however, only of academic interest, with little chances of real application. The more important developments in the two directions are treated below separately.

6.1 Non-standard positron emitters

In view of the enhancing significance of PET, considerable efforts have been devoted over the last 30 years towards development of a large number of non-standard, *i.e.* non-conventional positron emitters. There have been two motivations: a) study of slow metabolic processes; b) quantification of imaging and dosimetry. Two detailed review articles [6, 39] have recently been published on the development of about 25 novel positron emitters. In this article, therefore, only some salient features related to nuclear data work are discussed.

Out of all non-standard positron emitters recently developed, three radionuclides, *viz.* ^{64}Cu ($T_{1/2} = 12.7$ h), ^{124}I ($T_{1/2} = 4.2$ d) and ^{86}Y ($T_{1/2} = 16.0$ h), are finding worldwide application. They are opening new perspectives in radioimmunotherapy and radiation dosimetry. The commonly used production method in each case is the low-energy (p, n) reaction on the respective highly-enriched target nucleus. The basic data in all three cases were measured at the Forschungszentrum Jülich [40–42]. Although extensive development work related to targetry and chemical separation of those radionuclides has been done in many laboratories (for review cf. [6, 7]), only one new data measurement has been reported for the ^{64}Ni$(p, n)^{64}$Cu reaction [43]. On the other hand, for the three radionuclides under discussion, intermediate energy-reactions have been investigated by several groups [*cf*. 10, 41, 44–54] and data evaluation has also been performed [*cf*. 9, 10, 23, 55, 56]. Nonetheless, it is concluded that for each of those three radionuclides the respective (p, n) reaction gives the purest product, though the yield is not very high.

Besides the above mentioned three established non-standard positron emitters, there is great potential interest in other positron emitters as well, *e.g.* ^{72}As ($T_{1/2} = 26.0$ h), ^{73}Se ($T_{1/2} = 7.1$ h), ^{76}Br ($T_{1/2} = 16.2$ h), ^{89}Zr ($T_{1/2} = 78.4$ h), *etc.* Detailed reports on formation cross sections of several novel positron emitters *via* low and intermediate energy reactions have been published in recent years [*cf*. 57–62]. As an example, we consider the data for the production of ^{76}Br [59, 60]. An evaluation has been done [63] and from the recommended cross sections the yields of ^{76}Br *via* three reactions, namely ^{76}Se$(p, n)^{76}$Br, ^{77}Br$(p, 2n)^{76}$Br and ^{78}Se$(p, 3n)^{76}$Br, were calculated. The results are reproduced in Fig. 3. The method for production of this radionuclide could thus be chosen according to the proton energy available at the cyclotron. In practice, however, the ^{76}Se$(p, n)^{76}$Br reaction is preferred because of the lowest level of the ^{77}Br ($T_{1/2} = 56.0$ h) impurity.

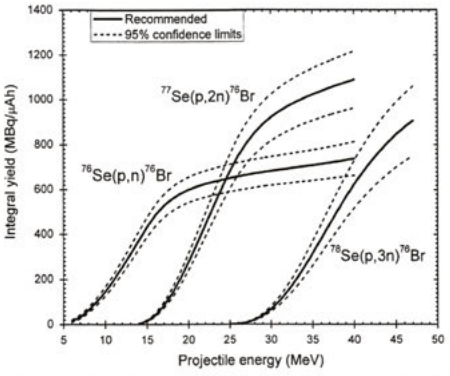

Fig. 3. Calculated integral yields for the ^{76}Se$(p, n)^{76}$Br, ^{77}Se$(p, 2n)^{76}$Br and ^{76}Se$(p, 3n)^{76}$Br reactions (after Ref. [63]).

Measurements have also been reported on parent radionuclides of some potentially useful positron emitting generator radionuclides (*e.g.* ^{44}Ti (60.4 a)/^{44}Sc (3.9 h)); ^{62}Zn (9.1 h)/^{62}Cu (9.7 min), *etc.* [64, 65]. Further extensive cross section data work on many radionuclides is continuing in several laboratories.

6.2 Novel therapeutic radionuclides

The new trend in internal radionuclide therapy is to make use of radionuclides emitting low-range but highly ionising radiation, *i.e.* low-energy alpha- and beta-particle emitters, X-ray emitters or Auger electron emitters. The topic has been discussed in some detail in a recent article [7]. In the present contribution, therefore, only a few selected aspects are dealt with.

Among the β^- emitters, the radionuclides ^{67}Cu ($T_{1/2} = 2.58$ d; $E_{\beta^-} = 577$ keV) and ^{186}Re ($T_{1/2} = 3.72$ d; $E_{\beta^-} = 1070$ keV) have been receiving enhanced attention. Radiochemical measurements [*cf*. 66] showed that a highly enriched ^{68}Zn target and the energy range $E_p = 70 \rightarrow 30$ MeV lead to ^{67}Cu of high quality. Two other new measurements on the reactions ^{64}Ni$(\alpha, p)^{67}$Cu [67] and ^{70}Zn$(d, \alpha n)^{67}$Cu [68] utilizing highly-enriched targets reveal that, similar to the ^{70}Zn$(p, \alpha)^{67}$Cu process [44], large scale production of ^{67}Cu *via* the two new routes is also not feasible. The necessity of a 70 MeV proton beam for the production of ^{67}Cu is thus imminent.

With regard to the production of ^{186}Re, the suggested method is the ^{186}W$(p, n)^{186}$Re reaction, though the ^{186}W$(d, 2n)^{186}$Re reaction has also been investigated and gives higher yield than the (p, n) reaction. Several measurements for the ^{186}W$(p, n)^{186}$Re reaction have been reported in recent years [*cf*. 69–74]. An analysis of those data was carried out [9, 75] and the result is given in Fig. 4. Calculations done using the three nuclear model codes, namely STAPRE, EMPIRE and TALYS, reproduce most of the data well [75]. From a critical discussion it was concluded [75] that for obtaining high-purity ^{186}Re, an enriched ^{186}W target is absolutely necessary and the maximum proton energy should not exceed 18 MeV.

Among the potentially useful X-ray and Auger electron emitters, the radionuclides ^{131}Cs ($T_{1/2} = 9.7$ d; X-rays), ^{140}Nd ($T_{1/2} = 3.37$ d; Auger electrons), ^{193m}Pt ($T_{1/2} = 4.33$ d; Auger electrons) and ^{195m}Pt ($T_{1/2} = 4.02$ d; Auger electrons) have attracted some attention. The radionuclide ^{131}Cs is of considerable promise for prostate cancer brachytherapy.

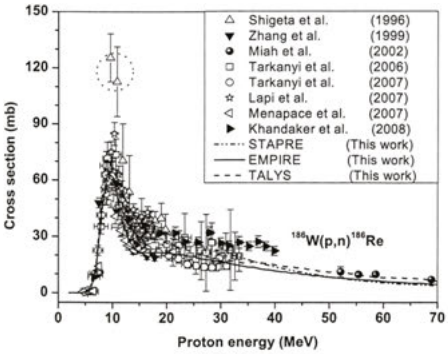

Fig. 4. Normalised experimental data and results of nuclear model calculations for the $^{186}W(p,n)^{186}Re$ reaction (after Ref. [75]).

Its effective production through the $^{131}Xe(p,n)^{131}Cs$ reaction has been demonstrated [*cf*. 76]. The radionuclide ^{140}Nd is interesting, not only because of its therapeutic effect but also because of its positron-emitting short-lived daughter ^{140}Pr ($T_{1/2} = 3.4$ min) which allows its localisation *via* PET imaging. Its production is carried out either by the $^{nat}Ce(^3He, xn)^{140}Nd$ process or through the $^{141}Pr(p, 2n)^{140}Nd$ reaction [*cf*. 77, 78]. Cross section data for its production *via* the $^{141}Pr(d, 3n)^{140}Nd$ reaction have also been reported [79].

The radionuclides ^{193m}Pt and ^{195m}Pt are pure X-ray and Auger electron emitters, each decay leading to more than 30 secondary electrons. Thus both those radionuclides have great potential in Auger electron therapy. In a recent study it could be shown that small amounts of ^{195m}Pt can be produced with high specific activity *via* the $^{192}Os(\alpha,n)^{195m}Pt$ reaction [80]. Using the same target but higher energy α-particles, on the other hand, it was found that ^{193m}Pt of high specific activity could be advantageously produced through the $^{192}Os(\alpha,3n)^{193m}Pt$ reaction [81]. Over the optimum energy range $E_\alpha = 40 \rightarrow 30$ MeV, this radionuclide can be produced in quantities sufficient for therapeutic applications.

Regarding targeted α-particle therapy, the radionuclide ^{211}At ($T_{1/2} = 7.2$ h; $E_\alpha = 5870$ keV) has been under investigation for quite some time. Its production data *via* the $^{209}Bi(\alpha,2n)^{211}At$ reaction are well known. Presently there is great demand for the radionuclide ^{225}Ac ($T_{1/2} = 10.0$ d; $E_\alpha = 5830$ keV) which is useful in itself as well as for providing ^{213}Bi ($T_{1/2} = 46$ min; $E_\alpha = 5900$ keV) through a generator system. In recent years some interest has also developed in ^{226}Th ($T_{1/2} = 31$ min; $E_\alpha = 6340$ keV) and ^{223}Ra ($T_{1/2} = 11.43$ d; $E_\alpha = 5720$ keV). Extensive effort is presently being invested in the development of ^{225}Ac. On one hand its separation from nuclear waste (^{229}Th) is being optimised and, on the other, the $^{226}Ra(p, 2n)^{225}Ac$ reaction, making use of the radioactive target material ^{226}Ra, is being developed [*cf*. 82]. A third possibility under investigation is its production *via* irradiation of ^{232}Th with intermediate energy protons [83–85]. The yield of ^{225}Ac and the level of the ^{227}Ac ($T_{1/2} = 21.8$ a) impurity calculated from the recently reported data [83] are given in Fig. 5. At a proton energy

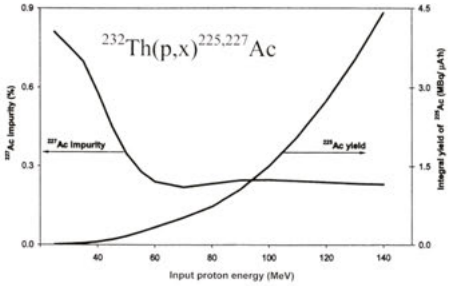

Fig. 5. Production yield of ^{225}Ac and level of ^{227}Ac impurity depending on inlet proton energy on a thick ^{232}Th target and outlet energy of 21 MeV (after Ref. [83]).

of 140 MeV the yield of ^{225}Ac amounts to 4.2 MBq/μA h which is lower than the value of about 7 MBq/μA h *via* the $^{226}Ra(p, 2n)^{225}Ac$ reaction. The advantage of the new route is that the use of the radioactive target ^{226}Ra is avoided. The disadvantages are: lower yield, need of an intermediate energy accelerator and extensive effort in chemical processing. Anyway, both the latter two methods need considerable further development.

The α-emitting radionuclide ^{223}Ra holds great promise for bone cancer therapy. It was obtained *via* the chain $^{226}Ra(n, \gamma)^{227}Ra$ (42.2 min) $\xrightarrow{\beta^-}$ ^{227}Ac (21.8 a) $\xrightarrow{\beta^-}$ ^{227}Th (18.7 d) $\xrightarrow{\alpha}$ ^{223}Ra. Another potentially interesting production route entails the irradiation of ^{232}Th with intermediate energy protons [*cf*. 83–85].

The production of ^{230}U (and its daughter ^{226}Th) has been studied *via* $^{231}Pa(p, 2n)^{230}U$, $^{231}Pa(d, 3n)^{230}U$ and $^{232}Th(p, 3n)^{230}Pa \xrightarrow{\beta^-} {}^{230}U$ processes [86–88]. The target material ^{231}Pa is radioactive; the chemical separation involved is thus very demanding [86].

7. Conclusions

Radionuclide production technology is well established and the relevant nuclear data for production of the commonly used radionuclides have been standardised. Yet some nuclear data activities are continuously underway to improve the quality of the products, *i.e.* either decrease the level of radioactive impurities or improve the specific activity of the product. In recent years, considerable effort has been devoted to searching for alternative routes for the production of ^{99m}Tc. The major thrust of the nuclear data research today is, however, towards developing non-conventional novel positron emitters and therapeutic radionuclides. The non-standard metallic positron emitters are opening new perspectives in radioimmunotherapy and quantitative radiation dosimetry. The use of low-range but highly ionising radiation in targeted therapy is attracting great attention. It is anticipated that nuclear data work related to the development of the two types of radionuclides will continue also in the future. Newer medical applications, *e.g.* multimode imaging, combination of radioactivity with nanotechnology, *etc.*, will demand novel radionuclides. For their production, applica-

tion of intermediate energy cyclotrons, accelerating all four light charged particles, *viz.* p, d, ^{3}He and ^{4}He, may be necessary. In particular, an intermediate energy α-particle beam holds great promise for producing high-spin isomers which decay by Auger electron emission and are thus potentially very interesting for Auger therapy.

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