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Nuclear data for production and medical application of radionuclides: Present status and future needs☆

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ABSTRACT

Introduction: The significance of nuclear data in the choice and medical application of a radionuclide is considered: the decay data determine its suitability for organ imaging or internal therapy and the reaction cross section data allow optimisation of its production route. A brief discussion of reaction cross sections and yields is given.
Standard radionuclides: The standard SPECT, PET and therapeutic radionuclides are enumerated and their decay and production data are considered. The status of nuclear data is generally good. Some existing discrepancies are outlined. A few promising alternative production routes of ^{99m}Tc and ^{68}Ga are discussed.
Research-oriented radionuclides: The increasing significance of non-standard positron emitters in organ imaging and of low-energy highly-ionizing radiation emitters in internal therapy is discussed, their nuclear data are considered and a brief review of their status is presented. Some other related nuclear data issues are also mentioned.
Production of radionuclides using newer technologies: The data needs arising from new directions in radionuclide applications (multimode imaging, theranostic approach, radionanoparticles, etc.) are considered. The future needs of data associated with possible utilization of newer irradiation technologies (intermediate energy cyclotron, high-intensity photon accelerator, spallation neutron source, etc.) are outlined.
Conclusion: Except for a few small discrepancies, the available nuclear data are sufficient for routine production and application of radionuclides. Considerable data needs exist for developing novel radionuclides for applications. The developing future technologies for radionuclide production will demand further data-related activities.

1. Introduction

1.1. Significance and overview

Radionuclides find application in many fields, their major use being in nuclear medicine, both in diagnosis and internal radiotherapy [1]. Each application, however, demands a special type of radionuclide, the choice being dependent on its decay properties. The two major physical considerations in internal use of radionuclides are:

(a) suitability for imaging.
(b) radiation dose caused to the patient.

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. In internal radionuclide therapy, on the other hand, a localized, well-defined radiation dose needs to be deposited in a malignant or inflammatory tissue to achieve the desired therapeutic effect. Thus, for in vivo diagnostic investigations involving organ imaging, radionuclides are required that do not cause much radiation dose and 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). Regarding the radiation dose, attention has to be paid to the emitted corpuscular radiation. The spectrum of radionuclides required in internal radionuclide therapy (endotherapy) is therefore very broad. In general, radionuclides emitting low-range highly-ionizing radiation, i.e. α or β^- particles, conversion and/or Auger electrons, are of great interest. Thus a complete set of decay data of a radionuclide is required to be able to calculate the radiation dose in a diagnostic or therapeutic medical application.

Besides the physical considerations mentioned above, the quality and availability of a radionuclide play an important role in its broad application. In this regard the production data, i.e. the nuclear reaction cross section data, are of great significance. As it is well known, the production of radionuclides is carried out using nuclear reactors as well as accelerators/cyclotrons. The reactor production generally leads to

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neutron excess radionuclides. They mostly decay by β^- emission and are therefore especially suited 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 [2]. In reactor production of radionuclides the nuclear reactions (n,γ), (n,f) and (n,p) are commonly utilized, and in cyclotron production, proton, deuteron, ^{3}He or α-particle induced reactions find application, though the use of proton induced reactions is more common. In recent years some attention has also been devoted to photon-induced reactions like (γ,n) and (γ,p).

The optimization of a production route is strongly dependent on an accurate knowledge of the relevant nuclear reaction cross section data. The major aim of optimization is to maximize the yield of the desired product and to minimize the impurity level. The latter is the most important criterion, and nuclear reaction data play a very important role in achieving a high radionuclidic purity of the product. Whereas non-isotopic impurities can be chemically removed, the change in the ratio of the desired radionuclide to an isotopic radioactive impurity is achieved only through the choice of a proper energy range of the projectile within the target material. Another consideration is the specific activity (which is defined as the radioactivity per unit mass of the element) of the radionuclide. Charged particle induced reactions generally lead to products of high specific activity whereas in neutron and photon induced reactions, particularly in (n,γ) and (γ,n) reactions, special techniques (e.g. use of precursor/generator system, Szilard Chalmer's process, etc.) are needed to increase the specific activity. The former involves the separation and use of the daughter radionuclide formed via β^- or EC decay of the nuclear reaction product. In the latter case, some of the recoiling radioactive atoms, following a nuclear reaction, are separated (from the bulk of the inactive target material) because of their occurrence in a different valence state as compared to the target atoms. The specific activity of the separated species is thus high but its yield amounts to only a small fraction of the total activity.

The above discussion shows that both radioactive decay data and reaction cross section data play important roles in the production and application of radionuclides in medicine. It should also be explicitly mentioned that the chemical form of the radionuclide and its biochemical behavior are perhaps of greater significance regarding the application. The scope of this review, however, is limited to nuclear data related to medical radionuclides. This subject has been treated during the last 30 years in many compilations, evaluations and review articles. In general, the decay data of medical radionuclides are being constantly improved under the auspices of the Society of Nuclear Medicine (SNM) of the USA and the standard publication MRID 2007 [3] encompasses about 500 radionuclides. Furthermore, the evaluated decay data files of the National Nuclear Data Center (NNDC), USA, describe the data for almost all the known radionuclides [4]. Nonetheless, some discrepancies and deficiencies still exist in individual cases.

Regarding the production data, a huge amount of information exists on neutron induced reactions [5], mainly due to their potential energy-related applications. Those data are very useful also for production of radionuclides in a nuclear reactor. In comparison, the database for charged-particle induced reactions, needed in cyclotron production of radionuclides, is not strong. Although during the last three decades extensive measurements have been reported from several laboratories around the world [6] and the database has been considerably strengthened, several critical reviews carried out periodically by this author [7–13] demonstrate the need of continuous charged-particle data work in relation to medical radionuclide development and applications, in particular because it is a dynamic field. As far as photon-induced reactions for medical radionuclide production are concerned, their database is weak [14].

1.2. Cross sections and yields

The formation of a radioactive product in irradiation of a target is described by the activation equation given below (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 reaction 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. Thus using the above equation, both the cross section of a reaction and the projectile flux can be determined, provided one of them is accurately known. In each case, however, the absolute activity of the product needs to be determined.

The quantitative assay of the induced radioactivity is commonly carried out by using one or more well-defined γ-rays (or other characteristic radiation) of the radionuclide, whereby the efficiency of the detector and the intensity of the γ-ray (or other radiation) used play vital roles. In particular, if a weak γ-ray with a large uncertainty in the intensity is used, the measured absolute activity (i.e. the disintegration rate) and therefore the calculated reaction cross section may entail large uncertainty. In fact the determination of the projectile flux and the measurement of the product radioactivity constitute the two major sources of uncertainty in the experimentally determined cross section of a nuclear reaction.

The techniques involved in neutron and photon induced reaction cross section measurements are somewhat similar. The charged-particle induced reaction cross section measurement, however, is more challenging [7] due to the following two reasons:

a) rapid loss of energy of the charged particle in the target (range–energy relationship).
b) rapid change of the reaction cross section with energy (excitation function).

The technique therefore consists of irradiation of a stack of thin samples of the target material (often of high isotopic enrichment, with thickness of each sample amounting to only a few μm) with a few monitor reaction foils inserted in between to determine the beam current (for more details [7]). The induced radioactivity in the target material as well as in the monitor foil is determined as described above. The loss of the projectile energy in the stack is calculated by a well-established code but uncertainties in the calculation influence both the energy scale and the cross section. Thus rather than using an average cross section, the individual cross sections effective over small energy ranges are considered. Due to the use of thin targets, the number of target nuclei in the path of the beam is relatively small but it must be known accurately, not only for obtaining high accuracy in the cross section but also in the projectile energy degradation calculation. The total uncertainty involved in charged-particle induced reaction cross section measurements is thus generally higher than in the neutron cross section work.

In charged-particle production of radionuclides the yield A (in Bq) for a certain energy range (E_1 to E_2) is calculated by a modified form of the activation equation given below [7]:

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

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 (particles s^{-1}), $\left(\frac{dE}{d(\rho\chi)}\right)$ the amount of the target material needed to decrease the projectile energy over a small range

($g\,cm^{-2}$), $\sigma(E)$ the cross section at energy E, λ the decay constant of the product, and t is the time of irradiation.

The calculated yield represents the maximum yield which can be expected from a given nuclear process under well-defined conditions. In practice, however, the experimentally obtained yields in high-current production runs are invariably lower than the calculated 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. Nonetheless, the yield calculated from the excitation function of a reaction serves as an ideal value for optimizing a production target system.

It should be pointed out that the experimentally determined cross sections by individual research groups need to be standardized for efficient use in the production of medical radionuclides. As mentioned above, extensive standardized data exist for neutron-induced reactions. For charged-particle induced reactions, however, only limited data, standardized under the auspices of the International Atomic Energy Agency (IAEA) [15,16] and some other groups (cf. for example [17]), are available.

1.3. Scope of present review

The present review deals with the status of nuclear data for both commonly used standard radionuclides and research-oriented novel radionuclides, pointing out inconsistencies and deficiencies, wherever possible. Furthermore, some radionuclides thought to be of value for potential applications are also considered and the related nuclear data are discussed. A few other nuclear data related issues are also mentioned. Finally, the future needs of data associated with the production of radionuclides via possible utilization of newer irradiation technologies (intermediate energy cyclotron, high-intensity photon accelerator, spallation neutron source, etc.), are briefly outlined.

2. Commonly used standard radionuclides

2.1. Diagnostic radionuclides

2.1.1. Standard radionuclides for SPECT and status of their nuclear data

The suitable γ-ray for SPECT-studies has an energy in the range of 100–200 keV. From a large number of γ-ray emitters of some interest in imaging using gamma cameras, only five radionuclides have found somewhat wider use in SPECT-studies. They are: ^{67}Ga ($T_{½}$ = 3.26 d), ^{99m}Tc ($T_{½}$ = 6.0 h), ^{111}In ($T_{½}$ = 2.8 d), ^{123}I ($T_{½}$ = 13.2 h) and ^{201}Tl ($T_{½}$ = 3.06 d). The radionuclide ^{99m}Tc is by far the most commonly used SPECT radionuclide. It emits a 141 keV γ-ray 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. Recent estimates reveal that worldwide about 40 million patients per year are investigated using this radionuclide. 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, namely ^{201}Tl, is extensively utilized for myocardial perfusion measurements. The remaining two radionuclides, i.e. ^{67}Ga and ^{111}In, are less commonly used as SPECT agents. They are now partly being considered for therapeutic applications because they emit a large number of Auger electrons. Somewhat similar is the case of ^{77}Br($T_{1/2}$ = 57.0 h). It was occasionally used in SPECT-studies but is now potentially important for Auger therapy.

The major decay data of the above mentioned radionuclides [3,4] are given in Table 1 and their status is mentioned. Regarding the production data, a large number of nuclear processes have been investigated, and the more commonly used ones have been recently reviewed [2,8]. In Table 1 therefore only the common production routes are given. In general, ^{99}Mo, the parent of ^{99m}Tc, is produced in a nuclear reactor via the fission of highly enriched ^{235}U. The other four radionuclides, namely ^{67}Ga, ^{111}In, ^{123}I and ^{201}Tl, on the other hand, are produced in high batch yields at a medium-sized cyclotron via (p,xn) reactions. The status of data of those reactions is generally good; only in the case of ^{123}I there are some discrepancies.

As mentioned above, some efforts have also been devoted to standardization of data of the most commonly used production routes of those radionuclides, especially under the auspices of the IAEA, and recommended cross sections are now available [15]. Some of the inconsistencies in the data of a few radionuclides mentioned in that report [15] have been addressed in a few recent measurements [18,19].

2.1.2. Standard radionuclides for PET and status of their nuclear data

The number of positron-emitting radionuclides is large. However, for routine PET investigations, mainly the short-lived "organic" positron emitters, viz. ^{11}C ($T_{½}$ = 20.4 min) and ^{18}F ($T_{½}$ = 110 min), and to a lesser extent ^{15}O ($T_{½}$ = 2.0 min) and ^{13}N ($T_{½}$ = 10.0 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 because it has a longer half-life, emits a low-energy positron and allows versatile chemistry. All four positron emitters can be produced in high batch yield at low-energy cyclotrons (E < 20 MeV) using low-energy nuclear reactions [1,2,8]. Besides those positron emitters, two other short-lived positron emitters, namely ^{68}Ga ($T_{½}$ = 67.6 min) and ^{82}Rb ($T_{½}$ = 1.3 min), widely used in diagnostic studies, are produced via generator systems. Their long-lived parents ^{68}Ge ($T_{½}$ = 271 d) and ^{82}Sr ($T_{½}$ = 25.3 d), respectively, are produced using intermediate energy protons, i.e. E_p = 30–100 MeV [20].

The major nuclear data of standard radionuclides for PET are also given in Table 1. Their status is similar to that of standard radionuclides for SPECT. The decay data are well-known [3,4]. Some improvements are, however, constantly underway, e.g. determination of half-life or γ-ray intensity with higher accuracy. Regarding production data, first evaluations of excitation functions of the most commonly used reactions performed in 2000 under the umbrella of the IAEA [15] showed that the status of data of ^{14}N(p,α)^{11}C, ^{16}O(p,α)^{13}N and ^{14}N(d,n)^{15}O reactions was quite satisfactory. For the reactions ^{18}O(p,n)^{18}F, ^{nat}Ge(p,xn)^{68}Ge and ^{nat}Rb(p,xn)^{82}Sr, however, more measurements were recommended. In the meantime, the older measurement on the first reaction [21] was augmented by a detailed study [22]. Also the other two reactions were further investigated [23,24] and the available database is now stronger. For a few less commonly used low-energy reactions, like ^{13}C(p,n)^{13}N and ^{15}N(p,n)^{15}O, on the other hand, the database is weak.

During the production of short-lived positron emitters using low-energy reactions, a few side-reactions also deserve some attention. Though they do not directly affect the production process, they contribute to the impurity level and so more detailed cross section measurements are recommended. In the production of ^{11}C via the ^{14}N(p,α)^{11}C reaction, for example, considerable amount of ^{13}N ($T_{½}$ = 10.0 min) is formed via the ^{14}N(p,d)^{13}N reaction. Recently it has been shown that large amounts of ^{14}O ($T_{½}$ = 1.15 min) are also formed via the ^{14}N(p,n)^{14}O reaction [25]. Similarly during the production of ^{15}O via the ^{14}N(d,n)^{15}O reaction, the ^{14}N(d,t)^{13}N is also possible [26], while during the production of ^{18}F through the most commonly used ^{18}O(p,n)^{18}F reaction, the reaction ^{18}O(p,t)^{16}O may occur. The two tritium emitting reactions have not been experimentally investigated. Their contributions are expected to be small but proper measurements of the respective excitation functions via tritium counting should be carried out to be able to estimate the total accumulated tritium during a given production run. The levels of other activation products formed in the target walls (e.g. Ti, Ni, Nb, Ag, etc.), on the other hand, have been often empirically investigated and found to be small.

2.2. Standard radionuclides for therapy and status of their nuclear data

As mentioned above, for internal radiotherapy β^-, α, Auger electron and X-ray emitters are of great interest [1,9]. The number of those radionuclides is very large, but only a limited number of them find practical application. The simplest case is brachytherapy which, is commonly performed with ^{192}Ir ($T_{½}$ = 73.8 d) in the form of a wire, ^{125}I ($T_{½}$ =

Table 1
Status of available nuclear data and further nuclear data needs related to commonly used standard diagnostic radionuclides.

Radio-nuclide	Decay data				Production data			
	$T_{½}$	Mode of decay (%)	Relevant emitted radiation; need for further data	Status of avail-able data	Common production process; need for further data	Energy range (MeV)	Typical batch yield (GBq)	Status of data; comment
A. SPECT radionuclides			E_γ: keV (%)[a]					
^{67}Ga	3.26 d	EC (100)	93 (37); 185 (20) Need exists for more detailed Auger electron spectra with regard to therapeutic application.	good	^{68}Zn(p,2n)^{67}Ga[e] ^{67}Zn(p,n)^{67}Ga[e,f]	26 → 18 15 → 8	50 3	good good
^{99m}Tc	6.0 h	IT (100)	141 (87) Need exists for more detailed Auger electron spectra with respect to microdosimetry.	good	^{235}U(n,f)^{99}Mo → ^{99m}Tc[e] ^{98}Mo(n,γ)^{99}Mo → ^{99m}Tc[f] *Alternative route in development* ^{100}Mo(p,2n)^{99m}Tc Need exists for extensive data on possible formation of impurities via ^{100}Mo(p,xn)^{97m,g,98,99g}Tc and $^{92\text{-}98}$Mo(p,xn)$^{93\text{-}99}$Tc reactions.	c d 22→10	>10^3 500 developing	good good good
^{111}In	2.8 d	EC (100)	171 (93); 247 (94) Need exists for more detailed Auger electron spectra with regard to therapeutic application.	good	^{112}Cd(p,2n)^{111}In[e] ^{111}Cd(p,n)^{111}In[e,f]	25 → 18 25 → 18	50 3	good good
^{123}I	13.2 h	EC(100)	159 (83) Need exists for more detailed Auger electron spectra with regard to microdosimetry.	good	^{123}Te(p,n)^{123}I[e,f] ^{124}Xe(p,2n)^{123}Cs → ^{123}Xe → ^{123}I[e] ^{124}Xe(p,pn)^{123}Xe → ^{123}I ^{124}Xe(p,2p)^{123}I Need exists for good measurements on ^{124}Xe(p,pn)^{123}Xe and ^{124}Xe(p,2p)^{123}I reactions. ^{127}I(p,5n)^{123}Xe → ^{123}I[f]	14.5 → 10 29 → 23 29 → 23 29 → 23 65 → 45	20 70[g] 40[g]	weak database good discrepancy not known reevaluation recommended
^{201}Tl	3.06 d	EC (100)	69-82 keV X-rays; 167 (10.2)	good	^{203}Tl(p,3n)^{201}Pb → ^{201}Tl ^{nat}Tl(p,xn)^{201}Pb → ^{201}Tl	28 → 20 28 → 20	70[h] 30[h]	good good
B. PET radionuclides			E_{β^+} in keV[b]					
^{11}C	20.4 min	β$^+$ (99.8) EC (0.2)	960	good	^{14}N(p,α)^{11}C Need exists for evaluation of data on impurity reactions ^{14}N(p,n)^{14}O, and ^{14}N(p,pn)^{13}N.	13 → 3	>100	good
^{13}N	10.0 min	β$^+$ (100)	1190	good	^{16}O(p,α)^{13}N ^{13}C(p,n)^{13}N[e,f]	16 → 7 15 → 8	30 10	good weak database
^{15}O	2.0 min	β$^+$ (99.9) EC (0.1)	1723	good	^{14}N(d,n)^{15}O Need exists for measurement on ^{14}N(d,t)^{13}N reaction beyond 12 MeV via tritium counting (related to waste treatment) ^{15}N(p,n)^{15}O[e,f]	8 → 0 12 → 0	100 80	good weak database
^{18}F	110 min	β$^+$ (97) EC (3)	635	good	^{20}Ne(d,α)^{18}F ^{18}O(p,n)^{18}F[e] Need exists for measurement on ^{18}O(p,t)^{16}O reaction via tritium counting (related to waste treatment)	14 → 0 16 → 3	30 150	good good
^{68}Ga	67.6 min	β$^+$ (90) EC (10)	1900[j]	good	^{nat}Ga(p,xn)^{68}Ge → ^{68}Ga *Alternative routes in development* ^{68}Ge(p,n)^{68}Ga[e] ^{65}Cu(α,n)^{68}Ga[e]	70 → 20 18 → 10 25 → 5	40[i] developing developing	good evaluation needed evaluation needed
^{82}Rb	1.3 min	β$^+$ (96) EC (4)	3350[k]	good	^{nat}Rb(p,xn)^{82}Sr → ^{82}Rb Need exists for more data on impurity reaction ^{nat}Rb(p,xn)^{85}Sr.	70 → 50	70[i]	good

[a] γ-ray is used in SPECT studies.
[b] Values refer to maximum β$^+$ energies in keV. For PET studies annihilation radiation is used.
[c] With reactor neutrons.
[d] With neutrons in a high flux reactor.
[e] Using highly enriched isotope as target material.
[f] Less commonly used nuclear process.
[g] ^{123}I yield after a 7 h decay of ^{123}Xe.
[h] ^{201}Tl yield after a 32 h decay of ^{201}Pb.
[i] Yield of parent of generator system.
[j] Associated 1077 keV γ-ray (3.0%).
[k] Associated 776 keV γ-ray (13.4%).

59.4 d) as a stent or ^{103}Pd ($T_{½}$ = 17.0 d) as a seed or a stent. In the case of ^{192}Ir, the strong β^- particles are effective but in the latter two cases, X-rays cause the therapeutic effect. A more common application is palliative therapy. Radionuclides like ^{32}P ($T_{½}$ = 14.3 d) and ^{90}Y ($T_{½}$ = 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 ($T_{½}$ = 9.4 d) with low β^- energy, is also used. A third variation of internal therapy with β^- emitters involves the radiosynthesis of tumor seeking agents. For this purpose the radionuclides ^{89}Sr ($T_{½}$ = 50.5 d), ^{153}Sm ($T_{½}$ = 1.9 d), ^{177}Lu ($T_{½}$ = 6.7 d), ^{188}Re ($T_{½}$ = 17.0 h) and ^{131}I ($T_{½}$ = 8.02 d) are more commonly used, the first four in case of bone metastases and the radionuclide ^{131}I in the form of iodide for treatment of thyroid tumors. Regarding the α-emitters, the application of ^{211}At ($T_{½}$ = 7.2 h) has a very long story, but is still in the research phase. The radionuclide ^{223}Ra ($T_{½}$ = 11.4 d) in the form of chloride is an approved drug in many jurisdictions. As far as Auger electron therapy is concerned, to date most of the experimental studies have been performed using ^{125}I.

As far as the nuclear data of standard therapeutic radionuclides are concerned, the status is comparable to that of diagnostic radionuclides. The decay data are in general well-known [3,4]. The production of those radionuclides is generally carried out in a nuclear reactor via the (n,f) or (n,γ) reaction. The former leads to products of high specific activity, e.g. ^{90}Sr and ^{131}I. The (n,γ) reaction product has low specific activity, unless use is made of its β^- or EC decay product, e.g. ^{130}Te(n,γ)^{131m,g}Te $\rightarrow^{\beta^-}$ ^{131}I, ^{124}Xe(n,γ)^{125}Xe $\rightarrow^{EC}$ ^{125}I, etc. In the case of brachytherapy, the specific activity of the radionuclide is not critical. For other internal therapeutic applications, however, high specific activity is strongly desired. In many cases, therefore, special production routes are used (cf. Table 2). For example, the production of the 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, and the data are known [27]. 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 the fission products. An alternative route for the production of ^{90}Y, namely the ^{90}Zr(n,p)^{90}Y reaction, has also been suggested [28] but not practically used so far. The parent ^{188}W on the other hand is produced by double neutron capture on ^{186}W in a high flux reactor. The radionuclides ^{103}Pd and ^{211}At are produced at a cyclotron via the reactions ^{103}Rh(p,n)^{103}Pd and ^{210}Bi(α,2n)^{211}At, respectively. In the case of ^{153}Sm, the ^{150}Nd(α,n)^{153}Sm reaction has been suggested [29] but not practically applied so far. The status of production data of all the above mentioned radionuclides is discussed below in detail (Section 2.4).

2.3. Alternative routes of production of standard radionuclides

There may be several motivations behind a search for alternative routes of production of standard radionuclides, e.g.,

- to increase the yield, radionuclidic purity or specific activity of the desired product,
- to achieve more security in the supply of the nuclide.

Two radionuclides, namely ^{99m}Tc and ^{68}Ga, are of timely interest and deserve special attention.

2.3.1. ^{99m}Tc

The apprehension of shortage in the supply of this most commonly used SPECT-radionuclide, due to possible shut-down of nuclear research reactors, has led to considerable scientific effort to develop alternative production methods for the parent radionuclide ^{99}Mo as well as the desired product ^{99m}Tc. In general, more use of accelerators has been proposed [30]. In this review consideration is given to the nuclear data of several alternative methods.

For the production of **^{99}Mo**, following routes independent of a reactor, are being considered.

a) Photon induced reactions ^{nat}U(γ,f)^{99}Mo and ^{100}Mo(γ,n)^{99}Mo. The cross sections are known for the present estimation of the ^{99}Mo yield [14,31]; however, development of production technology would demand construction of high-power accelerators, rather far from the present day technology. If the project makes progress, more extensive and precise data will be needed.
b) Neutron induced reaction ^{100}Mo(n,2n)^{99}Mo. The excitation function of the reaction is known fairly well [32–34] and the cross section at 14–15 MeV is high. However, similar to a high-power accelerator for producing photons, an intense 14 MeV DT-neutron source will have to be developed.
c) ^{nat}U(n,f)^{99}Mo and ^{232}Th(n,f)^{99}Mo processes induced by spallation neutrons [13]. The cross sections may be appreciable but

Table 2
Status of available nuclear data and further nuclear data needs related to some commonly used standard therapeutic radionuclides produced via unconventional routes.

Radionuclide	Decay data				Production data			
	$T_{½}$	Mode of decay (%)	Relevant emitted radiation; need for further data E_{β^-} in keV[a]	Status Of avail-able data	Production process; need for further data	Energy range (MeV)	Typical batch yield (GBq)	Status of available data; comment
^{32}P	14.3 d	β^- (100)	1710	good	^{32}S(n,p)^{32}P Need exists for better analysis of fine structures in the excitation function.	b	>100	good[c]
^{89}Sr	50.5 d	β^- (100)	1470	good	^{89}Y(n,p)^{89}Sr Stronger database in the energy region above 15 MeV is needed.	b	20	good[c]
^{90}Y	2.7 d	β^- (100)	2290	good	^{90}Zr(n,p)^{90}Y[d] Stronger database in the energy region above 15 MeV is needed.	b	in development	weak database
^{103}Pd	17.0 d	EC (100)	Auger electrons and X-rays Need exists for more accuracy in X-ray and weak γ-ray intensities	good	^{103}Rh(p,n)^{103}Pd ^{107}Ag(p,x)^{103}Pd	13 → 7 80 → 30	50 in development	good weak database
^{188}Re	17.0 h	β^- (100)	2110[e]	good	^{186}W(n,γ)^{187}W(n,γ)^{188}W → ^{188}Re Need exists for more accurate data on second neutron capture.	b	20	weak database

[a] Values refer to maximum β^- energies in keV.
[b] With fission neutrons in a high flux reactor.
[c] Integral data agree within 10% with data integrated from the excitation function.
[d] This is an alternative suggested production reaction. In general ^{90}Sr is isolated from fission products.
[e] Associated 155 keV γ-ray (14.9%).

are not known. These processes may be of considerable importance in the future. Extensive data needs will then arise.

d) Charged-particle induced reactions ^{100}Mo(p,pn)^{99}Mo and ^{100}Mo(d,p2n)^{99}Mo. Evaluated data for the former reaction [35] and a recent measurement on the latter reaction are available [36]. The cross section in the intermediate energy range of about 40 MeV is fairly high and hence the expected yield of ^{99}Mo is appreciable. It should, however, be pointed out that the production of ^{99}Mo from a ^{100}Mo target (whether using a photon, neutron or charged-particle induced reaction) would always lead to low specific activity and the generator column loaded with that ^{99}Mo would behave similar to that produced via the ^{98}Mo(n,γ)^{99}Mo reaction in a nuclear reactor. Furthermore, since the enriched target (^{100}Mo) is expensive, its recovery from the column would be mandatory. Presently some efforts are being invested by a US company to prepare a generator system making use of low specific activity ^{99}Mo (NorthStar's RadioGenix™).

In contrast to ^{99}Mo production discussed above, presently the direct production of **^{99m}Tc** at a cyclotron appears to be more promising. The production reaction ^{100}Mo(p,2n)^{99m}Tc was first suggested about 40 years ago [37]. A critical study of this reaction done at Jülich at the request of the IAEA had shown that this route using 22 MeV protons on a highly enriched ^{100}Mo target is worth considering for local production and consumption of ^{99m}Tc [38]. Over the last few years a large number of measurements have been reported, some of them with enhanced precision [39–41], and a critical evaluation of all data has been carried out [35] using a rigorous nuclear model analysis and statistical fitting procedure. The results are shown in Fig. 1 together with those for the formation of the other Tc-isotopes. From the evaluated excitation function of the ^{100}Mo(p,2n)^{99m}Tc reaction the production yield of ^{99m}Tc over the suitable energy range of $E_p = 22 \rightarrow 10$ MeV was calculated as 700 MBq/μAh. This yield is sufficient for production purposes and the method is being commercially developed in Canada. The status of the data of this reaction is now satisfactory.

Despite the promising nature of the ^{100}Mo(p,2n)^{99m}Tc reaction, a note of caution has been expressed [35] with respect to the level of radioactive and non-radioactive metallic impurities. As shown in Fig. 1, using even 100% enriched ^{100}Mo as target material, other expected products are ^{100}Tc ($T_{½} = 15.8$ s), ^{99g}Tc ($T_{½} = 2.1 \times 10^5$ a), ^{98}Tc ($T_{½} = 4.2 \times 10^6$ a) and ^{97g}Tc ($T_{½} = 4.0 \times 10^8$ a). In particular the level of ^{99g}Tc and ^{98}Tc may exceed that allowed by the present day pharmacopeia rules, especially if $E_p \approx 22$ MeV is used. If the ^{100}Mo used is of lower enrichment, many other isotopic radioactive impurities would also be formed. Thus for a full assessment of the feasibility of the production route under consideration, extensive nuclear data work is mandatory, involving nuclear reaction cross section measurements on various stable isotopes of molybdenum.

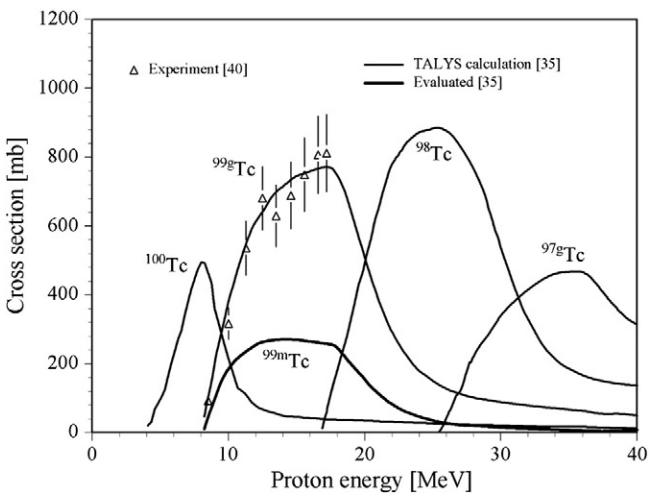

Fig. 1. Excitation functions of the reactions ^{100}Mo(p,n)^{100}Tc, ^{100}Mo(p,2n)^{99m,g}Tc, ^{100}Mo(p,3n)^{98}Tc and ^{100}Mo(p,4n)^{97g}Tc. The bold curve for the ^{100}Mo(p,2n)^{99m}Tc reaction is based on a rigorous evaluation of all available experimental data, whereas the other curves represent calculational results obtained using the code TALYS. Some available experimental data for the ^{100}Mo(p,2n)^{99g}Tc reaction [40] are also shown (diagram adapted from Ref. [35]).

2.3.2. ^{68}Ga

The generator system ^{68}Ge/^{68}Ga is commercially developed but the availability is rather limited. In view of the enhancing importance of ^{68}Ga, the idea is gaining significance to produce this radionuclide directly through the reaction ^{68}Zn(p,n)^{68}Ge at a small-sized cyclotron or the reaction ^{65}Cu(α,n)^{68}Ga at a medium-sized cyclotron [42]. The prospects for direct production of this radionuclide appear to be good, though the effort involved will be much more than in the generator elution. As far as nuclear data are concerned, several reports exist and a careful evaluation of all the available data is recommended.

2.4. Summary of data needs with respect to standard radionuclides

Based on the above discussion, two IAEA-CRP documents [15,16], several IAEA-Consultants' reports [43–45] and this author's own appraisal, a summary of the status of available data together with further/future needs related to commonly used standard diagnostic radionuclides is given in Table 1. The main decay data (half-life, γ-ray energies and intensities, the β^+ end-point energy and intensity, etc.) are well established and sufficient for routine patient-care investigations. More detailed information on Auger electron spectra, however, is needed, especially if any of the four SPECT-radionuclides, namely ^{67}Ga, ^{99m}Tc, ^{111}In and ^{123}I, is to be considered for use in Auger therapy. The need is more in case of ^{67}Ga, ^{111}In and ^{123}I because those radionuclides decay predominantly by EC, thereby emitting many Auger electrons, and have thus greater potential for therapeutic use. In the case of ^{99m}Tc, the major decay mode is internal transition with γ-ray emission, so that the role of Auger electrons, if any, has to be very carefully assessed.

Regarding the cross section data of the most commonly used production reactions, the status is good in many cases. For a few less commonly used production routes (not all given in Table 1), however, the status of data varies: some are good while for others the available database is generally weak. In those cases further experimental studies are recommended. For the production of ^{123}I, the excitation functions of the reactions ^{124}Xe(p,pn)^{123}Xe and ^{124}Xe(p,2p)^{123}I need to be carefully remeasured. With regard to the ^{127}I(p,5n)^{123}Xe reaction, a rigorous re-evaluation of the available data is recommended. As far as the four standard "organic" positron emitters (^{11}C, ^{13}N, ^{15}O and ^{18}F) are concerned, the emphasis with regard to their production has shifted to low-energy reactions given in Table 1 (with the status of their data). Some other low-energy reactions like ^{10}B(d,n)^{11}C, ^{10}B(α,n)^{13}N, ^{12}C(α,n)^{15}O or intermediate energy reactions like ^{16}O(p,pn)^{15}O, ^{nat}Ne(p,x)^{18}F, etc. are now seldom used. Their databases are also weak. In connection with the development of alternative routes of direct production of ^{99m}Tc, further nuclear data work is needed, especially with respect to the formation of both radioactive and stable impurities.

As regards standard therapeutic radionuclides, the decay data of the most commonly used ones like ^{90}Y, ^{125}I, ^{131}I, ^{153}Sm, ^{177}Lu, ^{192}Ir, etc. are well established [16]. They are generally produced in nuclear reactors via the common nuclear processes (n,f) and (n,γ) or (n,γ) followed by EC or β^- decay. The status of data of those processes is satisfactory. Regarding some radionuclides produced by special methods (cf. Table 2), the fission neutron-spectrum averaged cross sections of the (n,p) reactions are well documented [27]. The excitation functions of the (n,p) reactions [16,28] used, however, need some improvement because the integral data measured in a fission neutron field are not very consistent with those integrated using the excitation function and the fission

neutron spectrum. The database for the double neutron capture reaction $^{186}W(n,\gamma)^{187}W(n,\gamma)^{188}W$ is weak and further studies are necessary. Regarding the two cyclotron-produced commonly used therapeutic radionuclides, viz. ^{103}Pd and ^{211}At, the status of data of the $^{209}Bi(\alpha,2n)^{211}At$ reaction for production of ^{211}At is satisfactory [16]. For ^{103}Pd, however, some data needs exist, especially if the intermediate energy reaction $^{107}Ag(p,x)^{103}Pd$ would be used (for a review cf. [46]). As regards the suggested $^{150}Nd(\alpha,n)^{153}Sm$ reaction for the production of ^{153}Sm [29], the database is weak.

3. Research-oriented radionuclides

Besides routine production and application of standard radionuclides and radiopharmaceuticals for patient care, in recent years considerable work has been underway toward development of research-oriented novel radionuclides. The present emphasis is on development of two types of radionuclides, namely non-standard positron emitters for PET and highly-ionizing low-range radiation emitters for internal radiotherapy. A brief discussion of those radionuclides is given below and the status of nuclear data is discussed.

3.1. Non-standard positron emitters

A large number of positron emitters have been studied but about 25 of them are of more interest in medicine, especially because they allow investigation of slow metabolic processes and in some cases furnish the possibility of quantification of radiation dose in internal radiotherapy. Some aspects of their production and application have been reviewed [47–51,205]. In this article the emphasis is on nuclear data.

3.1.1. Status of decay data

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 long half-lives, (b) rather high positron end-point 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, in view of their increasing significance in PET studies, it has been recommended [43,44] to have a closer look at their decay data, i.e. the mass decay chains of all the useful and potentially useful non-standard positron emitters should be reevaluated and revised. The half-lives are well known but inconsistencies are observed in the intensities of the emitted positrons and some weak γ-rays. Though in a few cases new measurements [52–54] have been carried out and improved data on the positron emission intensities of ^{45}Ti, ^{64}Cu, ^{76}Br, ^{120}I and ^{124}I have been made available, for many other positron emitters further measurements are needed. The major non-standard positron emitters are listed in Table 3 together with their half-lives, positron emission intensities and most intense γ-rays (taken mostly from [3,4]). A few radionuclides emit only very weak γ-lines whose intensities are doubtful. Those cases are discussed below separately (cf. Section 4(a)). The nuclides for which large uncertainties exist in the positron branchings are ^{61}Cu, ^{66}Ga, ^{81}Rb, ^{82m}Rb, ^{83}Sr, ^{86}Y, ^{120g}I and ^{152}Tb [55]. The presently used values are only approximate, with uncertainties of up to 10% or even more.

It should be pointed out that the decay data of most of the non-standard positron emitters were determined in the context of nuclear structure studies and even recent evaluations are based on older data. Since many of the radioactive samples used in older measurements 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 electron capture (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 γγ-coincidence counting) and determination of the EC component via high-resolution X-ray spectroscopy using a thin Si(Li) detector [53]. The results for ^{64}Cu, taken from ref. [53] are given in Fig. 2 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. This author is convinced that evaluations of older data will not solve the problem. New precise measurements are absolutely necessary to determine the positron emission intensities of the radionuclides mentioned above.

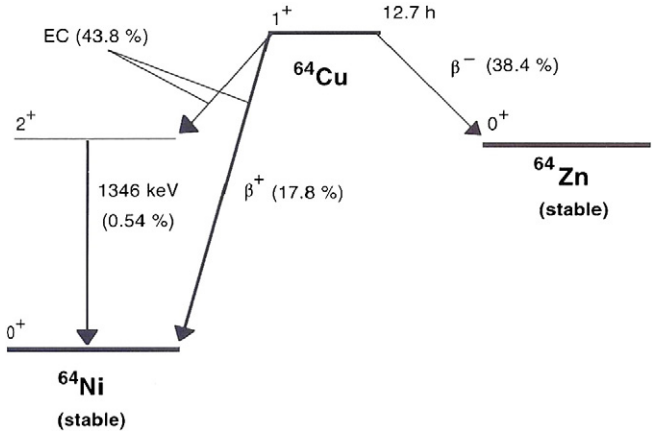

Fig. 2. Decay scheme of ^{64}Cu with intensities of emitted radiations (taken from Ref. [53]).

3.1.2. Production routes and status of cross section data

The production routes of non-standard positron emitters for which some sort of biological application has been demonstrated are listed in Table 3 [56–123]. Most of them can be produced using a small-sized 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 ^{45}Ti, ^{52}Mn, ^{61}Cu, ^{64}Cu, ^{66}Ga, ^{76}Br, ^{82m}Rb, ^{86}Y, ^{89}Zr, ^{90}Nb, ^{94m}Tc, ^{120}I and ^{124}I have been produced on a clinical scale using this route. Cross section measurements on the $^{44}Ca(p,n)^{44}Sc$ and $^{38}Ar(p,n)^{38}K$ reactions have also been reported, but clinical scale production has not been achieved. 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, e.g. ^{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, e.g. ^{75}Br, ^{76}Br via (^{3}He,xn)-reactions and ^{30}P, ^{38}K, ^{61}Cu and ^{73}Se via (α,xn)-reactions on relevant targets.

The fact that many of the non-standard positron emitters can be produced via the (p,n) reaction using low-energy cyclotrons 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 two conspicuous developments have been coming up, namely to install solid targetry [124] or to

Table 3
Some useful and potentially useful non-standard positron emitters, status of their available data[a] and further data needs.

Positron emitter	$T_{½}$	$I_{\beta+}$ [b] (%)	Major γ-ray energy in keV (%)	Nuclear reaction	Energy range (MeV)	Thick target yield[f] (MBq/μAh)	Major reference(s)	Status of production data; comment
Low energy range								
^{34m}Cl	32.2 min	54.0	146 (40.5)	^{36}Ar(d,α)[e]	8 → 3	252	[120]	sufficient till 8 MeV; beyond that weak database
^{38}K	7.6 min	99.4	2168 (99.9)	^{38}Ar(p,n)[e]	16 → 12	777	[56]	sufficient; single measurement
^{44}Sc	3.9 h	94.3	1157 (99.9)	^{44}Ca(p,n)[e]	18 → 6	2.3 × 10^3	[84,212,213]	sufficient; evaluation needed
^{45}Ti	3.1 h	85.7	719 (0.12)	^{45}Sc(p,n)	14.5 → 5	433	[57,58,84]	weak database
^{51}Mn	46.2 min	97.1	749 (0.26)	^{50}Cr(d,n)[e]	10 → 4	700	[59]	single measurement
^{52}Mn	5.6 d	29.6	1434 (100)	^{nat}Cr(p,x)	17 → 8	14	[60,61]	good; evaluation needed
^{55}Co	17.5 h	76.0	931 (75)	^{54}Fe(d,n)[e]	10 → 5	30	[62–65,66]	sufficient; data evaluated; some discrepancy
			477 (20)	^{58}Ni(p,α)[e]	15 → 7	14	[65,66]	good; data evaluated
^{61}Cu	3.3 h	62[c]	283 (12.5)	^{61}Ni(p,n)[e]	15 → 7	1418	[17,67,68,69]	good; data evaluated
				^{64}Zn(p,α)[e]	18 → 11	288	[68,69]	good; data evaluated
^{62}Cu	9.7 min	97.4	1173 (0.34)	^{62}Ni(p,n)[e]	14 → 10	1.3 × 10^4	[70]	single measurement
^{64}Cu	12.7 h	17.8[d]	1346 (0.54)	^{64}Ni(p,n)[e]	12 → 8	304	[67,71,72]	good; data evaluated
^{66}Ga	9.5 h	56[c]	1039 (38)	^{66}Zn(p,n)[e]	15 → 7	700	[73,74]	good; data evaluated
^{72}As	26.0 h	87.8	834 (79.5)	^{nat}Ge(p,xn)	22 → 8	114	[75,207]	weak database
^{75}Br	1.6 h	73.0	286 (92)	^{78}Kr(p,α)[e]	17 → 11	70	[76]	single measurement
				^{74}Se(d,n)[e]	12 → 8	509	[77]	single measurement
^{76}Br	16.2 h	58.2	559 (74)	^{76}Se(p,n)[e]	15 → 7	402	[78–80]	good; data evaluated
				^{78}Kr(d,α)[e]	13 → 4	0.06	[81]	single measurement
^{81}Rb	4.6 h	27[c]	190 (64.3)	^{80}Kr(d,n)[e]	14 → 6	372	[82]	single measurement
^{82m}Rb	6.5 h	21[c]	776 (84.5)	^{82}Kr(p,n)[e]	14.5 → 10	370	[83]	single measurement
^{86}Y	14.7 h	33[c]	1077 (82.5)	^{86}Sr(p,n)[e]	14 → 7	371	[84–86]	sufficient; data evaluated; some discrepancy
^{89}Zr	78.4 h	22.3	909 (100)	^{89}Y(p,n)	14 → 9	58	[87–89]	sufficient; evaluation needed
^{90}Nb	14.6 h	51.2	1129 (92.7)	^{90}Zr(p,n)[e]	15 → 8	423	[90,201–203]	sufficient; evaluation needed
^{94m}Tc	52 min	72.0	871 (94.2)	^{94}Mo(p,n)[e]	13 → 7	2 × 10^3	[91,122]	sufficient; single measurement
^{120g}I	1.3 h	56[c]	560 (73)	^{120}Te(p,n)[e]	15 → 9	2 × 10^3	[92]	sufficient; single measurement
^{124}I	4.18 d	22.0	603 (61)	^{124}Te(p,n)[e]	12 → 8	16	[93,94]	good; data evaluated
Intermediate energy range								
^{30}P	2.5 min	99.9	2235 (0.06)	^{27}Al(α,n)	28 → 10	ca. 1000	[95]	sufficient; single measurement
^{34m}Cl	32.2 min	54.0	146 (40.5)	^{32}S(α,d)	50 → 20	1608	[121]	weak database
^{38}K	7.6 min	99.4	2168 (99.9)	^{35}Cl(α,n)	22 → 7	ca. 400	[96,97]	weak database
				^{40}Ar(p,3n)	39 → 23	550	[98]	single measurement
^{44}Sc	3.9 h	94.3	1157 (99.9)	^{44}Ca(d,2n)[e]	25 → 10	2.5 × 10^3	[99,212]	single measurement
				^{45}Sc(p,2n)^{44}Ti[i] → ^{44}Sc[g]	35 → 15	0.004[h]	[99]	weak database
^{52}Fe	8.3 h	55.5	169 (99.2)	^{55}Mn(p,4n)	100 → 60	22	[100]	weak database
^{57}Ni	36.0 h	40	1378 (77.9)	^{59}Co(p,3n)	40 → 24	15	[101]	weak database
^{61}Cu	3.4 h	62[c]	283 (12.5)	^{59}Co(α,2n)	33 → 23	185	[69,102]	good; data evaluated
^{64}Cu	12.7 h	17.8[d]	1346 (0.54)	^{68}Zn(p,αn)[e]	30 → 20	116	[103,141]	weak database
^{72}As	26.0 h	87.8	834 (79.5)	^{75}As(p,4n) ^{72}Se → ^{72}As[g]	45 → 35	8[h]	[104,105]	weak database
				^{nat}Br(p,x)^{72}Se → ^{72}As[g]	100 → 70	3[h]	[204]	weak database
^{73}Se	7.1 h	65.4	361 (97)	^{75}As(p,3n)	40 → 30	1.4 × 10^3	[104,105]	sufficient; evaluation needed
				^{70}Ge(α,n)[e]	28 → 13	126	[106]	weak database
^{75}Br	1.6 h	73.0	286 (92)	^{75}As(^{3}He,3n)	36 → 25	278	[78,107]	weak database
				^{76}Se(p,2n)[e]	24 → 11	1.2 × 10^3	[78,108,109]	sufficient; evaluation needed
^{76}Br	16.2 h	58.2	559 (74)	^{75}As(^{3}He,2n)	18 → 10	11	[80,107,110]	good; data evaluated
^{77}Kr	1.2 h	84.0	130 (80)	^{79}Br(p,3n)[e]	40 → 30	7.4 × 10^3	[111,112]	weak database
				^{77}Se(^{3}He,3n)[e]	36 → 15	425		single measurement
^{81}Rb	4.6 h	27[c]	190 (64.3)	^{82}Kr(p,2n)[e]	27 → 19	1.8 × 10^3	[113]	sufficient; evaluation needed
^{83}Sr	32.4 h	26[c]	763 (30)	^{85}Rb(p,3n)[e]	37 → 30	160	[114]	single measurement
^{86}Y	14.7 h	33[c]	1077 (82.5)	^{88}Sr(p,3n)[e]	43 → 33	1.0 × 10^3	[84,86,115]	weak database
^{120g}I	1.3 h	56[c]	560 (73)	^{122}Te(p,3n)[e]	37 → 32	3.6 × 10^3	[116]	single measurement
^{124}I	4.18 d	22.0	603 (61)	^{125}Te(p,2n)[e]	22 → 15	93	[117]	single measurement
^{140}Pr	3.4 min	50.8	1596 (0.5)	^{141}Pr(p,2n)^{140}Nd → ^{140}Pr[g]	30 → 15	210[h]	[118,119]	weak database
^{152}Tb	17.5 h	18[c]	344 (57)	^{155}Gd(p,4n)[e]	70 → 30			no cross section available
				^{nat}Nd(^{12}C,xn)^{152}Dy → ^{152} Tb	110 → 80	ca 10[j]	[123,159]	weak database
				^{nat}Ta(p,spall)	~1000	ca 77[k]	[123,158]	weak database

[a] The decay data of all non-standard positron emitters are generally known, unless otherwise stated, but careful re-evaluations of mass decay chains are recommended (for more details see text). The very low intensity γ-rays of some radionuclides are discussed separately (Section 4a). The status of reaction data is given in the last column.
[b] This is the intensity of positrons in %; the rest is EC, unless otherwise stated.
[c] $I_{\beta+}$ value has rather large uncertainty.
[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] Calculated from the excitation function, unless otherwise stated.
[g] Generator system.
[h] Yield of parent.
[i] Uncertainty in the half-life of the parent.
[j] Experimental yield of parent (MBq/μAh).
[k] Experimental batch yield (MBq).

utilize an existing or modified liquid target for irradiating solutions of target isotopes [125–129]. In the latter case, care has to be taken to separate radiation induced chemical species. The yield of the desired radionuclide is generally low but it may be enough for local use.

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 (for details cf. reviews [47–51,205]. Further efforts are underway to assure large scale production of those radionuclides.

As regards the status of production data of non-standard positron emitters, it varies considerably from one case to another. For a few radionuclides, e.g. ^{52g}Mn, the available experimental database is fairly good and an evaluation of the data is needed. In a few other cases, the data for the commonly used production routes have been subjected to rigorous nuclear model analyses, e.g. for ^{55}Co [65], ^{61}Cu [17,69], ^{64}Cu [71], ^{66,68}Ga [74], ^{76}Br [80], ^{86}Y [86] and ^{124}I [94,130]. For the ^{54}Fe(d,n)^{55}Co and ^{86}Sr(p,n)^{86}Y reactions the nuclear model analysis showed considerable discrepancies with the experimental data. The results for the production of ^{86}Y via the ^{86}Sr(p,n) reaction are shown in Fig. 3 as an example [taken from Ref. [86]]. Among the experimental reports, [84,85,131,208], only Rösch et al. [85] published a detailed data set with full uncertainties. The data reported by Levkovskij [84] are extensive but without any experimental details or uncertainties. Furthermore, those data had to be reduced by a factor of 0.82 as recommended by Qaim et al. [35]. The experimental data are compared with the results of nuclear model calculations derived 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, the best fit to the experimental data being furnished by EMPIRE. It is evident that the scatter in the experimental data is large, and more precise measurements are called for, especially in view of the fact that this reaction has become the method of choice for the production of ^{86}Y (see above), whose importance is constantly increasing.

Several other non-standard positron emitters have also been produced via a low-energy reaction, i.e. a (p,n) or (d,n) process, and the available data appear to be sufficient, but they are generally based on single measurements. To this group belong the radionuclides ^{38}K, ^{51}Mn, ^{62}Cu, ^{75}Br, ^{81}Rb, ^{82m}Rb, ^{94m}Tc and ^{120}I. Although clinical scale production of several of those radionuclides has been achieved, there is certainly the need of strengthening the relevant databases. Furthermore, several of the above discussed positron emitters could also be produced via intermediate energy reactions for which the databases are not strong. The production of ^{152}Tb, a unique positron-emitting rare-earth radionuclide, has been attempted via two very special methods: (a) ^{12}C-ion induced reactions on ^{nat}Nd, producing ^{152}Dy which decays to ^{152}Tb. The final product was chemically separated [123]; (b) spallation of ^{nat}Ta with high-energy protons whereby the ^{152}Tb produced was first separated by an on-line mass separator and thereafter purified chemically [158]. The experimental yields for both the routes are given in Table 3. Further detailed cross section measurements are needed, especially on the ^{155}Gd(p,4n)^{152}Tb reaction which can be conveniently performed using a 100 MeV proton accelerator.

As far as the three comments, namely *single measurement, weak database and discrepancy*, given in Table 3 are concerned, they all stipulate and demand further measurements and evaluation of the data.

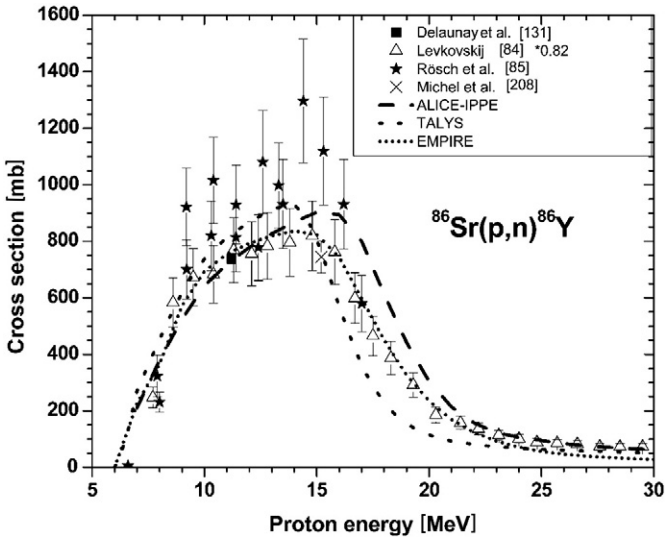

Fig. 3. Normalized experimental data for the ^{86}Sr(p,n)^{86}Y reaction along with the results of three nuclear model calculations, viz. ALICE-IPPE, TALYS and EMPIRE, plotted as a function of the proton energy (taken from Ref. [86]).

3.2. Novel therapeutic radionuclides: status of data and further needs

The number of potentially interesting therapeutic radionuclides is very large. However, as mentioned above, in internal radionuclide therapy the emphasis has been shifting over to low-range but highly-ionizing radiation emitters. The scope of this article is limited to eight radionuclides, namely ^{47}Sc, ^{67}Cu, ^{186}Re, ^{149}Tb, ^{225}Ac, ^{117m}Sn, ^{193m}Pt and ^{195m}Pt, which are presently attracting more attention. Among them the first three are β^- emitters, ^{149}Tb and ^{225}Ac are α-emitters, ^{117m}Sn emits low-energy conversion electrons, whereas ^{193m}Pt and ^{195m}Pt are Auger electron emitters. The decay characteristics [3,4] and main production routes of those radionuclides [132–173] are listed in Table 4. The inconsistencies and deficiencies in the data, if any, are pointed out and the need for further data is outlined. Each radionuclide is considered below individually.

3.2.1. ^{47}Sc

This radionuclide is gaining importance as a β^- theranostic pair of the β^+ emitter ^{44}Sc. Being a trivalent metal, Sc forms good chemical compounds which are potentially useful for therapy. The status of decay data of ^{47}Sc is good. The main nuclear reaction used for its production so far is the ^{47}Ti(n,p)^{47}Sc process on enriched target in a medium to high flux reactor and the production methodology has been well worked out [132–134]. The experimental fission-spectrum averaged cross section of this reaction is known [27]. However, the cross section obtained by integration of the reported excitation function [135] shows some discrepancy with the integrally measured cross section. The database of the excitation function above 15 MeV is weak and further work in this direction is recommended to remove the discrepancy. Some preliminary studies on the possibility of production of ^{47}Sc via the ^{48}Ti(γ,p)^{47}Sc and ^{48}Ca(γ,n)^{47}Ca → ^{47}Sc routes have also been reported [209,210] but as yet the database is rudimentary.

3.2.2. ^{67}Cu

This radionuclide is of considerable importance as a theranostic pair of the β^+ emitter ^{64}Cu. Since Cu exhibits excellent capacity to form organometallic compounds, the pair ^{64}Cu/^{67}Cu constitutes a very important theranostic system. The decay data of ^{67}Cu are sufficiently known [16] and its production methods have been reviewed [136]. Some of the reaction data have also been evaluated [16]. Presently four reactions are interesting from the practical point of view: (a) ^{67}Zn(n,p)^{67}Cu, (b) ^{68}Zn(γ,p)^{67}Cu, (c) ^{70}Zn(p,α)^{67}Cu and (d) ^{68}Zn(p,2p)^{67}Cu. They are discussed individually below.

The ^{67}Zn(n,p)^{67}Cu reaction using fission neutrons has been under investigation for more than 40 years. However, the chemical and radiochemical purities of ^{67}Cu achieved are not satisfactory. A recent study discusses the production of ^{64}Cu and ^{67}Cu in admixture for theranostic application [137]. The measured fission-spectrum averaged cross section of this reaction is well documented [27] but it shows some discrepancy with the value integrated from the excitation function which is known

Table 4
Some novel therapeutic radionuclides, status of available data and further needs.

Radionuclide	Decay data					Major production routes and relevant data				
	$T_{½}$	Radiation of interest (%)	Energy[a] (keV)	Major γ-ray energy in keV (%)	Status of decay data	Nuclear reaction	Energy range (MeV)	Thick target yield[b] (MBq/μAh)	Major reference(s)	Status of production data; comment
^{47}Sc	3.35 d	β^- (100)	610	159 (68)	good	^{47}Ti(n,p)[g]	fission spectrum	4.8×10^3/(g·h)[c]	[27,132–135]	weak database (> 15 MeV)
^{67}Cu	2.58 d	β^- (100)	577	185 (48.6)	good	^{67}Zn(n,p)	fission spectrum	0.44 /(g·h)[d]	[27,28,138]	weak database (> 15 MeV)
						^{68}Zn(γ,n)	photon source	1.0/(g·kW·h)[e]	[139]	weak database
						^{70}Zn(p,α)[g]	18 → 12	2.2	[16,84,142]	good; data evaluated
						^{68}Zn(p,2p)[g]	80 → 30	42	[16,143–145]	discrepancy
^{186}Re	3.78 d	β^- (92.5)	1070	137 (9.5)	good	^{186}W(p,n)[g]	18 → 5	4	[148–152]	good; data evaluated
		EC (7.5)				^{186}W(d,2n)[g]	18 → 9	16	[155–157]	weak database
^{149}Tb	4.1 h	α (16.7)	3970	165 (27.8)	sufficient	^{155}Gd(p,7n)[g]				no data available
		β^+ (4.3)		352 (33.0)		^{165}Ho(p,spall)	1000	5.8[f]	[123,158]	weak database
		EC (79)				^{142}Nd(^{12}C,5n)^{149}Dy → ^{149}Tb	100 → 80	2.5[f]	[123,159]	weak database
^{225}Ac	10.0 d	α (100)	5830	100 (1.7)	good	^{226}Ra(p,2n)	22 → 10	7	[161]	weak database
						^{232}Th(p,x)	140 → 60	4	[162–164]	sufficient; estimation of impurities needed
^{117m}Sn	13.6 d	IT (100)		159 (86.4)	good	^{nat}In(α,pxn)	45 → 20	0.3×10^{-3}	[168,169]	weak database
		Conversion electrons	156			^{116}Cd(α,3n)[g]	60 → 30	8.4	[168–170]	sufficient till 40 MeV; weak database (> 40 MeV)
^{193m}Pt	4.33 d	IT (100)		136 (0.11)	sufficient	^{192}Pt(n,γ)[g]	fission spectrum	i, h	[5]	sufficient
		Auger electrons	10–130			^{192}Os(α,3n)[g]	40 → 30	10	[172]	single measurement
^{195m}Pt	4.02 d	IT (100)		99 (11.4)	sufficient	^{194}Pt(n,γ)[g]	fission spectrum	i, h	[5]	sufficient
		Auger electrons	10–130			^{193}Ir(n,γ)^{194}Ir	fission spectrum		[5]	sufficient
						^{194}Ir(n,γ)^{195m,g}Ir → ^{195m}Pt	fission spectrum	j		big uncertainty
						^{192}Os(α,n)[g]	28 → 15	0.1	[172,173]	weak database

[a] For β^-, the values are maximum energies.
[b] Calculated from the excitation function, unless otherwise stated.
[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 batch 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).

well up to 15 MeV [138] but is discrepant at higher energies [28]. Further work on the excitation function is therefore recommended.

In recent years there has been an increasing interest in the utilization of electron linear accelerators for medical radionuclide production and the reaction $^{68}Zn(\gamma,p)^{67}Cu$ has been investigated in some detail [139]. The yield of ^{67}Cu from a ^{nat}Zn target amounts to about 1.0 MBq/(g·kW·h), and is rather low. Regarding the nuclear data, in addition to some more integral measurements, work is also necessary on the excitation function of this process.

Among the two charged particle induced reactions, the low energy $^{70}Zn(p,\alpha)^{67}Cu$ reaction has been practically used [140,141] but the cost of highly enriched ^{70}Zn target is high and the ^{67}Cu yield is low. The nuclear reaction cross section data on the other hand are reliable [84,142] and have been evaluated [16]. The $^{68}Zn(p,2p)^{67}Cu$ reaction appears to be the most promising for the production of ^{67}Cu. The measured cross sections, however, are somewhat discrepant [143–145] and theory does not reproduce the experimental data well [16,143]. It is a relatively high-yield process and ^{67}Cu could be produced in batches of a few GBq [146] using a high-current enriched ^{68}Zn target and a proton energy range of $E_p = 80 \rightarrow 30$ MeV. In view of the importance of this reaction, further precise cross section measurements are recommended. Though several studies appear to be underway in a few laboratories, a careful evaluation of the new data will be necessary.

3.2.3. ^{186}Re

The chemistry of Re is similar to that of Tc and since a large number of Tc-compounds are already being applied in nuclear medicine, the radionuclide ^{186}Re is attractive for internal radiotherapy. The intensities of the weak γ-rays emitted in its decay have been recently remeasured [147] and the status of other decay data is now regarded as good. This radionuclide was originally produced via the $^{185}Re(n,\gamma)^{186}Re$ reaction which has, however, now been superseded by the $^{186}W(p,n)^{186}Re$ process. Most of the studies deal with nuclear reaction cross sections [148–151]; only in a few papers small scale production has also been reported. A critical theoretical analysis showed [152] 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. Based on nuclear model calculations the specific activity of ^{186}Re was also predicted [152]. Some recent experimental work in this direction [153,154] appears to support the theoretical considerations. The status of cross section data for this reaction thus appears to be good. This radionuclide can also be produced via the $^{186}W(d,2n)^{186}Re$ reaction [153,155–157]. The yield of ^{186}Re through this route is higher than through the (p,n) reaction. The database, however, is weak.

3.2.4. ^{149}Tb

This is a rather exotic α-emitting lanthanide and has so far found only limited application. However, due to the relatively low energy of the α-particle and the good complex chemistry of lanthanides, it is of great potential interest in α-targeted therapy. The decay properties are sufficiently known, but more detailed information, especially on the branching ratios of various decay modes, is needed. For its production two nuclear routes, namely $^{165}Ho(p,spall)^{149}Tb$ and $^{142}Nd(^{12}C,5n)^{149}Dy \rightarrow {}^{149}Tb$, have been suggested [123,158,159]. In the first, ^{149}Tb was separated by an on-line mass separator and in the latter, radioterbium was chemically separated. The yields in both the processes are low but the applicability of the radionuclide in tracer studies was demonstrated [158]. The nuclear reaction database is weak and more detailed investigations are needed. A possible third alternative route, namely $^{155}Gd(p,7n)^{149}Tb$, has to date not been investigated. It could be induced by about 120 MeV protons, and the cross section is expected to be high.

3.2.5. ^{225}Ac

Considerable interest has been aroused in recent years in this α-emitting radionuclide. It is useful in itself as well as for providing ^{213}Bi ($T_{½} = 46$ min; $E_\alpha = 5900$ keV) through a generator system. The decay data involved in the relevant decay chain have been evaluated [16] and the half-life of ^{225}Ac was recently re-determined [160]. Regarding its production, presently extensive efforts are underway. On one hand its separation from nuclear waste is being optimized and, on the other, two nuclear routes, namely $^{226}Ra(p,2n)^{225}Ac$ and $^{232}Th(p,spall)^{225}Ac$, are being investigated. The first route requires the use of the radioactive target ^{226}Ra and the spallation route puts a heavy demand on the chemical processing. The calculated yield of ^{225}Ac via the $^{226}Ra(p,2n)$-reaction over $E_p = 22 \rightarrow 10$ MeV amounts to 7 MBq/μAh [161] and that via the spallation route over $E_p = 140 \rightarrow 60$ MeV amounts to 4 MBq/μAh [162,163]. Both the latter accelerator methods of production require further development work, especially with regard to the determination of impurities [164,165].

3.2.6. ^{117m}Sn

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 ($I_\gamma = 86.4\%$). This radionuclide was therefore initially of interest for SPECT studies. In later years the interest changed because the emitted quasi-monoenergetic conversion electrons of energy 156 keV are well-suited for internal therapeutic applications. In fact ^{117m}Sn is unique among all beta emitting radionuclides. It has found application in bone pain palliation studies and radiosynovectomy [166,167]. For its production several nuclear processes have been reported [for review cf. [13]. In general, attempts have been made to obtain no-carrier-added ^{117m}Sn via ^3He- and α-particle induced reactions on isotopes of In and Cd [168–170], as well as via proton induced reactions on Sb [214]. The integral yields of ^{117m}Sn are shown in Fig. 4 as a function of the projectile energy. The yields of the $^{115}In(\alpha,d)^{117m}Sn$ and $^{116}Cd(^3He,2n)^{117m}Sn$ reactions were calculated from the excitation functions reported for natural targets [169] after extrapolation to 100% enrichment of the target, thereby assuming the contributions of the $^{113}In(\alpha,\gamma)^{117}Sb \rightarrow {}^{117m}Sn$ and $^{114}Cd(^3He,\gamma)^{117m}Sn$ processes as negligible. Those yields are rather low (curves C and B, respectively). On the other hand, the yield of ^{117m}Sn calculated from the excitation function of the $^{116}Cd(\alpha,3n)^{117m}Sn$ reaction is fairly high (curve A). In this case the data reported by Adam Rebeles et al. [170] up to 43 MeV for enriched ^{116}Cd target were adopted: at higher energy the data by Qaim and Döhler [169] on ^{nat}Cd, extrapolated to 100% enrichment of ^{116}Cd, were used, assuming the contribution of the $^{116}Cd(\alpha,n)^{117m}Sn$ process at higher energies to be <5%. With

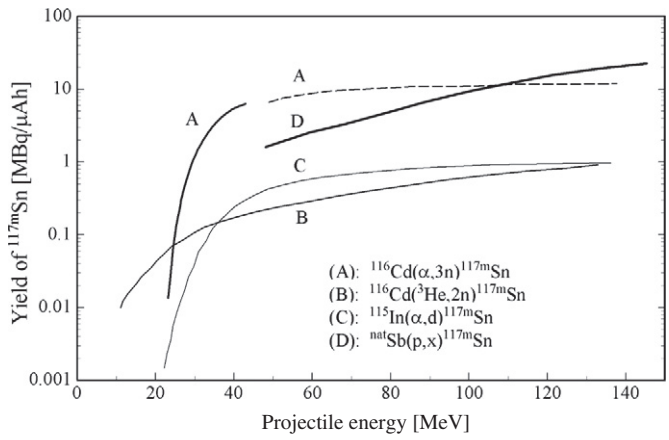

Fig. 4. Integral yields of ^{117m}Sn calculated from the excitation functions of the reactions, A: $^{116}Cd(\alpha,3n)$; B: $^{116}Cd(^3He,2n)$; C: $^{115}In(\alpha,d)$. The reported data for natural targets [169] were normalized to 100% enrichment of the respective target isotope (for more details see text), except for the curve A up to 43 MeV which is based on the data given in Ref. [170] for enriched ^{116}Cd. The curve D describes the experimental yield of the reaction $^{nat}Sb(p,x)^{117m}Sn$ [214].

regard to the $^{nat}Sb(p,x)^{117m}Sn$ process, the yields given in Fig. 4 are experimental values [214]. As discussed recently in detail [171], because of the high nuclear spin of the isomeric state, the α-particle induced reaction $^{116}Cd(\alpha,3n)^{117m}Sn$ has a high cross section, resulting in high yield. For the proton-induced reaction, the yield is higher, but energies of about 100 MeV are needed and the level of the radionuclidic impurity ^{113}Sn is high. The $^{116}Cd(\alpha,3n)^{117m}Sn$ reaction on a highly enriched ^{116}Cd target has therefore become the method of choice for commercial production of ^{117m}Sn [167]. The database, however, is still weak, especially above 40 MeV and further detailed measurements are needed.

3.2.7. ^{193m}Pt and ^{195m}Pt

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. Since platinum complexes (like cis-di-chlorodiaminplatinum) have been in use in chemotherapy as potent anti-tumor 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 widespread use was their non-availability with a high specific activity. The nuclear routes attempted for their production are listed in Table 4 and the status of the available data is mentioned. The $^{192}Pt(n,\gamma)^{193m}Pt$ reaction even while using enriched target leads to low specific activity. The production via the $^{192}Os(\alpha,3n)^{193m}Pt$ reaction on a highly enriched target appears to be very promising [172]. The cross section of the reaction is fairly high, mainly due to the favorable population of the high-spin $(13/2^+)$ ^{193m}Pt. Over the energy range $E_\alpha = 40 \rightarrow 30$ MeV the yield of ^{193m}Pt amounts to 10 MBq/μAh and the specific activity is high. The database, however, needs further strengthening.

As regards ^{195m}Pt, the $^{194}Pt(n,\gamma)^{195m}Pt$ reaction gives a product of low specific activity and the yield of the $^{192}Os(\alpha,n)^{193m}Pt$ process is also low [172,173]. The double neutron capture by ^{193}Ir, followed by β^- decay of the product $^{195m,g}Ir$ to ^{195m}Pt has not been fully investigated, though it appears to have a great potential. The production database is thus weak and further work is recommended.

Summarizing the status of nuclear data of novel therapeutic radionuclides, it appears that the decay data are fairly reliable, though in a few cases some more detailed information is needed. Regarding the production data, however, there is considerable need of new measurements as well as of evaluation of the existing data.

4. Some other nuclear data issues related to medical radionuclides

As mentioned above, the decay data of a radionuclide have to be sufficiently known before it can be selected for a diagnostic or a therapeutic medical application. However, there are often uncertainties, some of which have been discussed above, in particular those related to positron emission intensities, Auger electron spectra and intensities of some strong γ-rays. There is yet another issue, namely the γ-rays of very low intensities. This is discussed below. As regards the production data, they determine whether the product could meet the three criteria for application, namely sufficient yield, good radionuclidic purity and high specific activity (see discussion above). A few further issues related to the production aspect are also discussed below.

4.1. Very low-intensity γ-rays

Some of the medical radionuclides emit γ-rays of very low intensity. This is particularly the case for five non-standard positron emitters and two therapeutic radionuclides listed below:

^{45}Ti ($T_{½} = 3.08$ h; $E_\gamma = 720$ keV; $I_\gamma = 0.12\%$);
^{51}Mn ($T_{½} = 46.2$ min; $E_\gamma = 749$ keV; $I_\gamma = 0.26\%$);
^{62}Cu ($T_{½} = 9.7$ min; $E_\gamma = 1173$ keV; $I_\gamma = 0.34\%$);
^{64}Cu ($T_{½} = 12.7$ h; $E_\gamma = 1346$ keV; $I_\gamma = 0.54\%$);
^{140}Pr ($T_{½} = 3.4$ min; $E_\gamma = 1596$ keV; $I_\gamma = 0.5\%$);
^{103}Pd ($T_{½} = 17.0$ d; $E_\gamma = 357$ keV; $I_\gamma = 0.0221\%$);
^{211}At ($T_{½} = 7.2$ h; $E_\gamma = 687$ keV; $I_\gamma = 0.246\%$).

Normally such a weak γ-ray is of little consequence in the application of the respective radionuclide. However, some authors take the easy way and use that γ-ray to determine the absolute decay rate and therefore the formation cross section of the radionuclide (see Section 1.2). This may entail large uncertainty in the result. It is strongly advisable to cross check the obtained result for a β^+ emitter by carrying out β^+ counting or by measurement of the annihilation radiation via γγ-coincidence counting. For the therapeutic radionuclide ^{103}Pd, a cross check via X-ray spectrometry is recommended, and for ^{211}At both X-ray spectrometry and α-counting should be applied.

4.2. Use of multiparticle cyclotrons

As described above, 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, and the above mentioned three criteria (yield, purity, specific activity) are easily met. Although in many cases a large number of proton, deuteron, ^3He- and α-particle induced reactions have been attempted, for example for ^{64}Cu (for a review cf. [71]) and ^{124}I (for reviews cf. [94,130]), the choice usually remains on the (p,n) reaction because it leads to the highest purity product. On the other hand, the production of the SPECT-radionuclides (see Section 2.1.1) 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 needed [171], e.g. for ^{38}K, ^{117m}Sn, ^{211}At, etc. Similarly, the use of a deuteron beam appears to be attractive for the production of a few radionuclides since the (d,2n) reaction cross section in the medium to high mass region is generally higher than that of the (p,n) reaction. On the other hand, the (d,n) reaction product is a disadvantage while using the (d,2n) reaction, especially if it is a long-lived radionuclide. The production of ^{124}I via the $^{124}Te(d,2n)$-reaction, for example, leads to appreciable amount of the 60 d ^{125}I impurity, formed via the $^{124}Te(d,n)$-reaction. Due to this reason, the (d,2n) production method for ^{124}I was abandoned. The production of ^{103}Pd and ^{186}Re via the (d,2n) reaction in comparison to the presently used (p,n) reaction is, however, being favored because the (d,n) reaction products on the respective targets ^{103}Rh and ^{186}W are stable. It should, however, be pointed that the deuteron energies available at the 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, in connection with further development of research-oriented radionuclides, medium-sized multiparticle cyclotrons will continue to play an important role. The demand on the related nuclear data work will therefore also continue in the future.

4.3. 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, ^{201}Tl, etc.), ^{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. In the case of $^{73m,g}Se$ and $^{86m,g}Y$, for example, the isomeric states are short-lived and the application of the ground state radionuclide may start after complete decay of the metastable state. 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 which gives the lowest impurity level. As an example, the production of ^{94m}Tc was studied in three reactions [91,174,175], 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. This reaction was therefore adopted as the method of choice [176–178].

In contrast to isomeric states in non-standard positron emitters, an isomeric state within a therapeutic radionuclide may constitute an ideal source of radioactivity (e.g. ^{117m}Sn, ^{193m}Pt, as discussed above). 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.

There is yet another case of isomeric states where the medically interesting radionuclide is short-lived as compared to the much longer half-life of the isomeric state. Four important examples of this case are ^{99m,g}Tc, ^{177m,g}Lu, ^{186m,g}Re and ^{192m,g}Ir. A brief discussion of each pair follows. The isomeric pair ^{99m,g}Tc is well studied: ^{99m}Tc ($T_{½}$ = 6.0 h) is obtained via the decay of the parent ^{99}Mo ($T_{½}$ = 66.0 h) and the content of ^{99g}Tc ($T_{½} = 2.1 \times 10^5$ a) is negligible. The amount of ^{99g}Tc will certainly be higher in direct production of ^{99m}Tc, e.g. via the ^{100}Mo(p,2n) reaction [35]. In the case of ^{177m,g}Lu, the isotope of interest is ^{177g}Lu ($T_{½}$ = 6.7 d) whereas the long-lived ^{177m}Lu ($T_{½}$ = 160 d) is a disturbing activity. The direct production via the ^{76}Lu(n,γ)-reaction leads to a mixture of the two isomers and the specific activity of the product is low. An alternative indirect route, namely ^{176}Yb(n,γ)^{177}Yb → ^{177m,g}Lu, not only gives ^{177g}Lu of high specific activity but also the content of ^{177m}Lu is much lower [179]. A similar result was recently obtained in the activation of Yb with the deuteron [206]. The directly formed ^{177g}Lu in the ^{176}Yb(d,n)^{177m,g}Lu process was very small, but following the decay of the product ^{177}Yb, which is formed via the ^{176}Yb(d,p)^{177}Yb reaction, the purity of ^{177g}Lu was much higher. Regarding ^{186m,g}Re, the ground state is shorter lived ($T_{½}$ = 3.78 d) and it is of therapeutic interest, whereas the metastable state has a long half-life ($T_{½} = 2.0 \times 10^5$a). Its effect on the specific activity of ^{186}Re, produced via the ^{186}W(p,n) or ^{186}W(d,2n) reaction has been extensively discussed [152] and found to be negligible. As regards the pair ^{192m,g}Ir, the shorter lived ground state ($T_{½}$ = 73.8 d) is used in radiotherapy, and the longer lived metastable state ($T_{½}$ = 241 a) is an undesired impurity. Its content in production via the ^{191}Ir(n,γ) and ^{192}Os(p,n) reactions was estimated [180] and found to be negligible.

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.

4.4. Evaluation and validation of charged-particle induced reaction data

As mentioned above, attempts are underway in many laboratories to evaluate the existing experimental charged-particle data to be able to report recommended data. However, the evaluation methodology is still developing. Furthermore, before recommendation of the data to the user, a validation of the evaluated data is essential. The relevant methodology for validation is also as yet not developed. One option is to compare the evaluated data obtained from enriched isotopic targets with those from the natural element, after appropriate normalizations. This method was utilized in the validation of evaluated production data for ^{124}I [94], ^{76}Br [80] and ^{67}Ga [74]. A second option is [114] 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, i.e. a simple yield measurement in a production run is not sufficient (see Section 1.2). This type of nuclear data validation work related to charged-particle activation of materials for medical radionuclide production is expected to gain more importance in the future.

5. New directions in radionuclide applications and relevant nuclear data needs

Besides diagnostic and therapeutic studies using individual radionuclides, in recent years some new trends have been emerging with respect to application of radionuclides. They include:

- Quantification of SPECT-radiopharmaceuticals
- Theranostic approach
- Multimode imaging
- Radioactive nanoparticles

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 ^{99m}Tc-radiopharmaceuticals, labeling of the compound was performed using the non-standard positron emitter ^{94m}Tc ($T_{½}$ = 52 min), followed by a PET measurement (for example, cf. [178,181]). Similarly, for quantification of ^{123}I-radiopharmaceuticals, the use of a short-lived positron-emitting radioiodine, e.g. ^{120}I ($T_{½}$ = 1.3 h) may be advantageous.

The theranostic approach entails a combination of diagnosis and internal radionuclide therapy. Combining a β^- (or Auger electron) and β^+ emitting pair of radionuclides, 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 after mixing it with the positron emitter ^{86}Y [182]. This concept is now finding increasing application. There are several such pairs, e.g. ^{47}Sc/^{44}Sc; ^{67}Cu/^{64}Cu; ^{67}Ga/^{68}Ga or ^{66}Ga; ^{89}Sr/^{83}Sr; ^{131}I/^{124}I and ^{161}Tb/^{152}Tb. The status of nuclear data of most of those radionuclides has been discussed above. Further development of those pairs to reach the real stage of application would demand considerable effort, involving also some work related to nuclear data. In recent years there is some tendency to handle only one radionuclide as a theranostic agent, especially if it is readily available. One example is ^{177g}Lu. The dosimetry is based on γ-ray spectrometry and the therapeutic effect is well known. However, in comparison to the PET technique, simple γ-ray spectrometry is not quantitative. As discussed above, the nuclear data of the presently considered radionuclides for this purpose are generally well known but in some special cases further needs may arise.

The multimode imaging involves a combination of two or more organ-imaging techniques. The PET (and recently to some extent also SPECT) is being coupled with X-ray tomography (CT) and magnetic resonance imaging (MRI). The radionuclides of potential interest for the latter combination are considered here. 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 radionuclides ^{51}Mn and ^{52}Mn have been suggested. In recent years, however, there has been emphasis on ^{52}Mn [60,61,183–185,211] and authentic tracers labeled with ^{52g}Mn have been prepared [186,187]. As regards gadolinium, no positron-emitting radionuclide is available. In that case either SPECT (utilizing ^{147}Gd [188]) and MRI could be combined, or Gd could be converted to a so-called "intelligent (responsive) agent" [189] by chemically binding it with a metal like Cu through pyridine [190]; 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 yet another 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. The metals of interest are Fe and Ni and the potentially useful positron emitters could be ^{52}Fe and ^{57}Ni, respectively. Thus in view of the increasing significance of multimode imaging, the need for further development of suitable novel positron emitters will

increase and with that also the need for higher accuracy of the relevant nuclear data.

The use of radionanoparticles in medicine constitutes a long-term perspective, provided that the toxicity problems are overcome. The expectation is to ensure a more effective delivery of the radionuclide, through the use of nanoparticles, to the organ or tissue under investigation than that through a normal pharmaceutical. In animal studies, some limited applications of nanotargeted materials in imaging and therapy have been demonstrated [191–193] but further extensive development is needed. The types of radionuclides needed would generally be the same as in conventional diagnosis and therapy, so that the nuclear data needs should be covered within the areas discussed above.

6. Development of newer irradiation technologies for medical radionuclide production and relevant nuclear data needs

It is expected that also in the near future the radionuclide production technology will strongly depend on research reactors as well as small and medium-sized cyclotrons, often accelerating multiple particles, to energies up to about 30 MeV. In the medium to long term range, however, newer irradiation facilities in the following three directions are expected to be developed.

- Intermediate energy proton accelerators
- High-energy and high-intensity photon sources
- Spallation neutron sources

The possible use of those facilities in medical radionuclide production would lead to nuclear data needs discussed below.

6.1. 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, especially at Brookhaven and Los Alamos National Laboratories (USA), TRIUMF (Canada), iThemba LABS (South Africa) and Institute for Nuclear Research (INR) in Moscow (Russia). Some interesting or potentially interesting radionuclides whose production requires intermediate energy protons are listed in Tables 3 and 4. In general, the nuclear database is weak. With the expected increasing significance of some of those radionuclides, e.g. ^{52}Fe, ^{57}Ni, ^{67}Cu, ^{149}Tb, ^{152}Tb, ^{225}Ac, etc., some other laboratories may also build suitable high-intensity accelerator facilities, leading to more intensified efforts in this direction. Consequently, with the developing irradiation technology, the nuclear data needs are expected to increase continuously.

In a few limited laboratories the spallation process with 500–1000 MeV protons has also been studied to produce radionuclides. However, to date no radionuclide is produced via this method in sufficient quantity and acceptable quality for broader use. In recent years, the spallation process combined with an on-line mass separator has been utilized to produce a few novel radionuclides in small quantities for tracer studies [123,158]. Its scope is, however, very limited. As far as nuclear data are concerned, the production cross sections and yields of those radionuclides need to be accurately measured.

6.2. High energy photon sources

These sources are very much under discussion and several groups are working on development of high-intensity sources. A 50 MeV electron beam from an accelerator falling on a heavy metal target delivers photons with an energy spectrum extending from about 0.1 MeV to 50 MeV[194]. Over this energy range 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
^{nat}U(γ,f)^{99}Mo

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

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 [14]. The threshold of a (γ,p) reaction in the same mass region lies at approximately 10 MeV, the excitation function has a broad maximum between 20 and 30 MeV, with a cross section value of about 10 mb [14]. 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. As discussed in Section 2.3, the information available on the ^{100}Mo(γ,n)^{99}Mo reaction [14,31,200] is satisfactory for the present day calculations. For other (γ,n) and (γ,p) reactions, however, the available experimental database is weak, being limited only to some yield measurements [139,209,210]. Thus extensive studies using quasi-monoenergetic γ-rays are needed to be able to obtain reliable excitation functions. For integral studies, on the other hand, the photon spectrum generated in the interaction of 50 MeV electrons with a heavy metal [194] is quite suitable. It is thus recommended to perform also integral cross section measurements on the above mentioned nuclear reactions and to compare the data with the integrated values obtained using the photon spectral distribution and the excitation function of the reaction under consideration, as it has been done in the case of (n,p) reactions induced by reactor neutrons (see Section 2.2). As regards the photofission process, the available nuclear data for the formation of ^{99}Mo are satisfactory.

A consideration of the cross sections of various photon-induced processes mentioned above suggests that using the present day photon sources it is not feasible to produce any of the above mentioned 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 by a factor of about 10^4 higher than in the presently available accelerators. This would compensate for the low cross section and would boost up the batch yield. Two major advantages of the photon-induced reactions as compared to the charged-particle induced reactions are that large thick samples can be irradiated and heat dissipation is no problem. Some work in the utilization of photons has been reported with respect to the production of ^{47}Sc and ^{67}Cu (see Section 3.2), and further studies in several laboratories are continuing. 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.

6.3. Spallation neutron sources

These sources constitute a long term perspective for production of some medical radionuclides. In general, the irradiation of a heavy mass target with protons of energies above about 150 MeV leads to a so-called spallation neutron spectrum, the energy of which extends from about thermal up to the maximum energy of the proton, with a strong component covering the energy region of 0.5 to 10 MeV. In a high-intensity spallation neutron source, about 1000 MeV protons at a beam current of about 1 mA fall on a Pb/U target, whereby the neutron fluxes generated are comparable to those in a medium to high flux reactor [195]. Thus except for energy production, a spallation neutron source may be useful for all other reactor applications, including radionuclide production.

Due to the much harder spectrum of the spallation neutrons as compared to that of the fission neutrons, it is expected that with spallation neutrons several neutron threshold reactions would be advantageously induced, in particular the (n,p) reaction, whose greater part of the excitation function lies in the region of 3 to 10 MeV. On the basis of this idea a few mock-up experiments were performed [28,196] with 14 MeV d(Be) neutrons, whose average energy amounts to about 3 MeV, which is rather close to the average energy of spallation neutrons [195]. Using those neutrons, the measured cross sections of several (n,p) reactions were found to be by a factor of about 3 higher than with fission neutrons [28,196]. Based on the above results and also on our other experience with fast neutrons [197–199], it is suggested to explore the possibility of production of several medical radionuclides via the (n,p) reaction induced by spallation neutrons, e.g.

$^{32}S(n,p)^{32}P$; $^{35}Cl(n,p)^{35}S$; $^{47}Ti(n,p)^{47}Sc$; $^{64}Zn(n,p)^{64}Cu$;

$^{67}Zn(n,p)^{67}Cu$; $^{89}Y(n,p)^{89}Sr$; $^{90}Zr(n,p)^{90}Y$; $^{105}Pd(n,p)^{105}Rh$;

$^{149}Sm(n,p)^{149}Pm$, $^{153}Eu(n,p)^{153}Sm$; $^{159}Tb(n,p)^{159}Gd$;

$^{161}Dy(n,p)^{161}Tb$; $^{166}Er(n,p)^{166}Ho$; $^{169}Tm(n,p)^{169}Er$;

$^{175}Lu(n,p)^{175}Yb$; $^{177}Hf(n,p)^{177}Lu$, etc.

The production potential of ^{47}Sc using spallation neutrons was recently mentioned [215] and the possibility of production of several other radionuclides using spallation neutrons was also discussed [216]. In addition, spallation neutrons could be used to induce fission of ^{232}Th or ^{238}U to produce ^{99}Mo [13], thereby avoiding criticality problem associated with the fission of highly enriched ^{235}U.

It should, however, be emphasized that fast neutron spectral sources are not yet developed for application in medical radionuclide production. Extensive amount of nuclear data will be needed to characterize and standardize the neutron spectra prior to measurement and validation of the production-related integral data [217,218]. The main advantages of spallation neutrons as compared to fission neutrons would be higher yield and higher specific activity of the (n,p) and other neutron threshold reaction products.

7. 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, i.e. 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 small 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, ^{67}Ga, ^{111}In and ^{123}I, etc., 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.

It is somewhat astonishing that the list of radionuclides for medical applications has still not reached a saturation level. Very occasionally some novel radionuclide is shown to have some sort of medical application, especially in recent years in the case of metallic radionuclides. Relevant studies for its production in a radionuclidically pure form then start, including nuclear data activities. With the increasing newer applications under theranostic approach, multimode imaging or a combination of radioactivity with nanotechnology, the need for extended and reliable nuclear databases will also increase.

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 spallation neutrons for the production of some therapeutic radionuclides also deserves special attention. Thus new vistas are expected to open up in the future with respect to the development of radionuclide production technology. The supporting nuclear data research will therefore continue to play an important role.

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