CHAPTER 4

RADIONUCLIDE PRODUCTION

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4.1. THE ORIGINS OF DIFFERENT NUCLEI

All matter in the universe has its origin in an event called the 'big bang', a cosmic explosion releasing an enormous amount of energy about 14 billion years ago. Scientists believe that particles such as protons and neutrons, which form the building blocks of nuclei, were condensed as free particles during the first seconds. With the decreasing temperature of the expanding universe, the formation of particle combinations such as deuterium (heavy hydrogen) and helium occurred. For several hundred million years, the universe was plasma composed of hydrogen, deuterium, helium ions and free electrons. As the temperature continued to decrease, the electrons were able to attach to ions, forming neutral atoms and converting the plasma into a large cloud of hydrogen and helium gas. Locally, this neutral gas slowly condensed under the force of gravity to form the first stars. As the temperature and the density in the stars increased, the probability of nuclear fusion resulting in the production of heavier elements increased, culminating in all of the elements in the periodic table that we know today. As the stars aged, consuming their hydrogen fuel, they eventually exploded, spreading their contents of heavy materials around the universe. Owing to gravity, other stars formed with planets around them, composed of these heavy elements. Four and a half billion years have passed since the planet Earth was formed. In that time, most of the atomic nuclei consisting of unstable proton–neutron combinations have undergone transformation (radioactive decay) to more stable (non-radioactive) combinations. However, some with very long half-lives remain: ^{40}K, ^{204}Pb, ^{232}Th and the naturally occurring isotopes of uranium.

The discovery of these radioactive atoms was first made by Henri Becquerel in 1896. The chemical purification and elucidation of some of the properties of radioactive substances was further investigated by Marie Skłodowska-Curie and her husband Pierre Curie. Since some of these long lived radionuclides generated more short lived radionuclides, a new scientific tool had been

discovered that was later found to have profound implications in what today is known as nuclear medicine. George de Hevesy was a pioneer in demonstrating the practical uses of the new radioactive elements. He and his colleagues used a radioactive isotope of lead, ^{210}Pb, as a tracer (or indicator) when they studied the solubility of sparingly soluble lead salts. De Hevesy was also the first to apply the radioactive tracer technique in biology when he investigated lead uptake in plants (1923) using ^{212}Pb. Only one year later, Blumengarten and Weiss carried out the first clinical study, when they injected ^{212}Bi into one arm of a patient and measured the arrival time in the other arm. From this study, they concluded that the arrival time was prolonged in patients with heart disease.

4.1.1. Induced radioactivity

In the beginning, nature was the supplier of the radioactive nuclides used. Isotopes of uranium and thorium generated a variety of radioactive heavy elements such as lead, but radioactive isotopes of light elements were not known. Marie Curie's daughter Irène, together with her husband Frédéric Joliot took the next step. Alpha emitting sources had long been used to bombard different elements, for example, by Ernest Rutherford who studied the deflection of α particles in gold foils. The large deflections observed in this work led to the conclusion that the atom consisted of a tiny nucleus of protons with orbiting electrons (similar to planets around the sun). However, Joliot–Curie also showed that the α particles induced radioactivity in the bombarded foil (in their case, aluminium foil). The induced radioactivity had a half-life of about 3 min. They identified the emitted radiation to be from ^{30}P created in the nuclear reaction ^{27}Al(α, n)^{30}P.

They also concluded that:

> "These elements and similar ones may possibly be formed in different nuclear reactions with other bombarding particles: protons, deuterons and neutrons. For example, ^{13}N could perhaps be formed by capture of a deuteron in ^{12}C, followed by the emission of a neutron."

The same year, this was proved to be true by Ernest Lawrence in Berkeley, California and Enrico Fermi in Rome. Lawrence had built a cyclotron capable of accelerating deuterons up to about 3 MeV. He soon reported the production of ^{13}N with a half-life of 10 min. Thereafter, the cyclotron was used to produce several other biologically important radionuclides such as ^{11}C, ^{32}P and ^{22}Na. Fermi realized that the neutron was advantageous for radionuclide production. Since it has no charge, it could easily enter into the nucleus and induce a nuclear reaction. He immediately made a strong neutron source by sealing up ^{232}Ra gas

with beryllium powder in a glass vial. The α particle emitted from ^{232}Ra caused a nuclear reaction in beryllium and a neutron was emitted, ^{9}Be(α, n)^{12}C.

Fermi and his research group started a systematic search by irradiating all available elements in the periodic system with fast and slow neutrons to study the creation of induced radioactivity. From hydrogen to oxygen, no radioactivity was observed in their targets, but in the ninth element, fluorine, their hopes were fulfilled. In the following weeks, they bombarded some 60 elements and found induced radioactivity in 40 of them. They also observed that the lighter elements were usually transmuted into radionuclides of a different chemical element, whereas heavier elements appeared to yield radioisotopes of the same element as the target.

These new discoveries excited the scientific community. From having been a rather limited technique, the radioactivity tracer principle could suddenly be applied in a variety of fields, especially in life sciences. De Hevesy immediately started to study the uptake and elimination of ^{32}P phosphate in various tissues of rats and demonstrated, for the first time, the kinetics of vital elements in living creatures. Iodine-128 was soon after applied in the diagnosis of thyroid disease.

This was the start of the radiotracer technology in biology and medicine as we know it today.

One early cyclotron produced nuclide of special importance was ^{11}C since carbon is fundamental in life sciences. Carbon-11 had a half-life of only 20 min but by setting up a chemical laboratory close to the cyclotron, organic compounds labelled with ^{11}C were obtained in large amounts. Photosynthesis was studied using $^{11}CO_2$ and the fixation of carbon monoxide in humans by inhaling ^{11}CO. However, 20 min was a short half-life and the use of ^{11}C was limited to the most rapid biochemical reactions. It must be remembered that the radio-detectors used at that time were primitive and that the chemical, synthetic and analytical tools were not adapted to such short times. A search to find a more long lived isotope of carbon resulted in the discovery in 1939 of ^{14}C produced in the nuclear reaction ^{13}C(d, p)^{14}C.

Unfortunately, ^{14}C produced this way was of limited use since the radionuclide could not be separated from the target. However, during the bombardments, a bottle of ammonium nitrate solution had been standing close to the target. By pure chance, it was discovered that this bottle also contained ^{14}C, which had been produced in the reaction ^{14}N(n, p)^{14}C.

The deuterons used in the bombardment consist of one proton and one neutron with a binding energy of about 2 MeV. When high energy deuterons hit a target, it is likely that the binding between the particles breaks and that a free neutron is created in what is called a ‘stripping reaction’. The bottle with ammonium nitrate had, thus, unintentionally been neutron irradiated. Since no carbon was present in the bottle (except small amounts from solved airborne

carbon dioxide), the ^{14}C produced this way was of high specific radioactivity. It was also very easy to separate from the target. In the nuclear reaction, a 'hot' carbon atom was created, which formed $^{14}CO_2$ in the solution. By simply bubbling air through the bottle, the ^{14}C was released from the target.

The same year, tritium was discovered by deuteron irradiation of water. One of the pioneers 'Martin Kamen' stated:

> "Within a few months, after the scientific world had somewhat ruefully concluded that development of tracer techniques would be seriously handicapped because useful radioactive tracers for carbon, hydrogen, oxygen and nitrogen did not exist, ^{14}C and ^{3}H were discovered".

Before the second world war, the cyclotron was the main producer of radionuclides since the neutron sources at that time were very weak. However, with the development of the nuclear reactor, that situation changed. Suddenly, a strong neutron source was available, which could easily produce almost unlimited amounts of radioactive nuclides including biologically important elements, such as ^{3}H, ^{14}C, ^{32}P and ^{35}S, and clinically interesting radionuclides, such as ^{60}Co (for external radiotherapy) and ^{131}I, for nuclear medicine. After the war, a new industry was born which could deliver a variety of radiolabelled compounds for research and clinical use at a reasonable price.

However, accelerator produced nuclides have a special character, which makes them differ from reactor produced nuclides. Today, their popularity is increasing again. Generally, reactor produced radionuclides are most suitable for laboratory work, whereas accelerator produced radionuclides are more useful clinically. Some of the most used radionuclides in nuclear medicine, such as ^{111}In, ^{123}I and ^{201}Tl, and the short lived radionuclides, ^{11}C, ^{13}N, ^{15}O and ^{18}F, used for positron emission tomography (PET), are all cyclotron produced.

4.1.2. Nuclide chart and line of nuclear stability

During the late 19th century, chemists learned to organize chemical knowledge into the periodic system. Radioactivity, when it was discovered, conflicted with that system. Suddenly, various samples, apparently with the same chemical behaviour, were found to have different physical qualities such as half-life, emitted type of radiation and energy. The concept of 'isotopes' or elements occupying the 'same place' in the periodic system (from the Greek 'ίσος τόπος' (isos topos) meaning 'same place') was introduced by Soddy 1913, but a complete explanation had to await the discovery of the neutron by Chadwick in 1932.

The periodic system was organized according to the number of protons (atom number) in the nucleus, which is equal to the number of electrons to balance the atomic charge. The nuclide chart consists of a plot with the number of neutrons in the nucleus on the x axis and the number of protons on the y axis (Fig. 4.1).

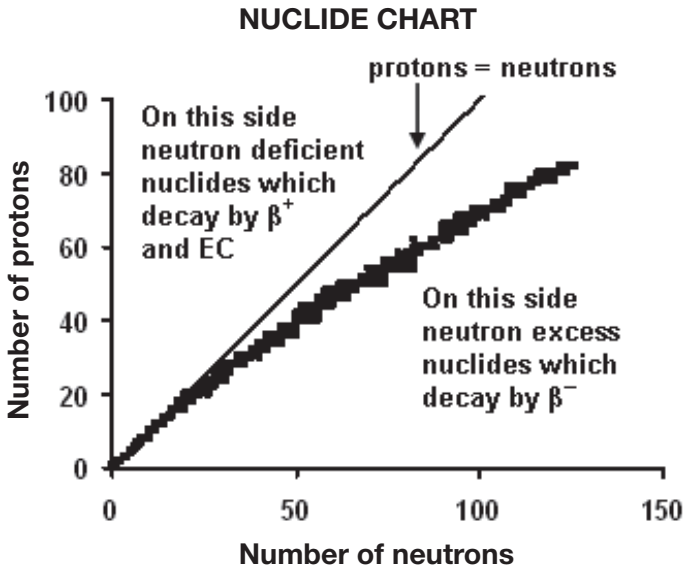


FIG. 4.1. Chart of nuclides. The black dots represent 279 naturally existing combinations of protons and neutrons (stable or almost stable nuclides). There are about 2300 proton/neutron combinations that are unstable around this stable line.

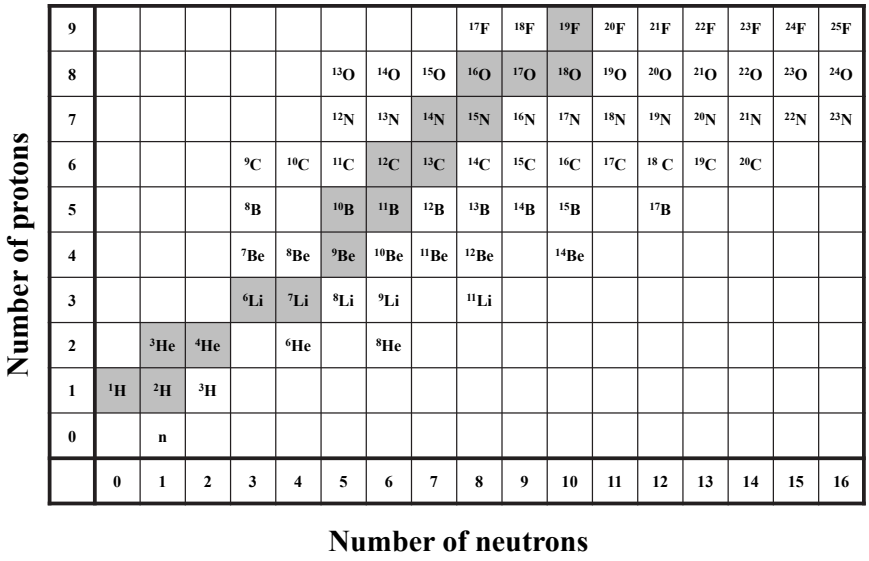
Figure 4.2 shows a limited part of the nuclide chart. The formal notation for an isotope is ${}^{A}_{Z}\mathrm{X}$, where X is the element name (e.g. C for carbon), A is the mass number ($A = Z + N$), Z is the number of protons in the nucleus (atom number) and N the number of neutrons in the nucleus.

The expression above is overdetermined. If the element name X is known, so is the number of protons in the nucleus, Z. Therefore, the simplified notation ${}^{A}\mathrm{X}$ is commonly used.

Some relations of the numbers of protons and neutrons have special names such as:

— Isotopes: the number of protons is constant (Z = constant).
— Isotones: the number of neutrons is constant (N = constant).
— Isobars: The mass number is constant (A = constant).

Of these expressions, only the isotope concept is generally used. It is important to understand that whenever the expression ‘isotope’ is used, it must always be related to a specific element or group of elements, for example, isotopes of carbon (e.g. ^{11}C, ^{12}C, ^{13}C and ^{14}C).



9									^{17}F	^{18}F	^{19}F	^{20}F	^{21}F	^{22}F	^{23}F	^{24}F	^{25}F
8						^{13}O	^{14}O	^{15}O	^{16}O	^{17}O	^{18}O	^{19}O	^{20}O	^{21}O	^{22}O	^{23}O	^{24}O
7						^{12}N	^{13}N	^{14}N	^{15}N	^{16}N	^{17}N	^{18}N	^{19}N	^{20}N	^{21}N	^{22}N	^{23}N
6				^{9}C	^{10}C	^{11}C	^{12}C	^{13}C	^{14}C	^{15}C	^{16}C	^{17}C	^{18}C	^{19}C	^{20}C		
5				^{8}B		^{10}B	^{11}B	^{12}B	^{13}B	^{14}B	^{15}B		^{17}B				
4				^{7}Be	^{8}Be	^{9}Be	^{10}Be	^{11}Be	^{12}Be		^{14}Be						
3				^{6}Li	^{7}Li	^{8}Li	^{9}Li		^{11}Li								
2		^{3}He	^{4}He		^{6}He		^{8}He										
1	^{1}H	^{2}H	^{3}H														
0		n															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

FIG. 4.2. A part of the nuclide chart where the lightest elements are shown. The darkened fields represent stable nuclei. Nuclides to the left of the stable ones are radionuclides deficient in neutrons and those to the right, rich in neutrons.

In the nuclide chart (Fig. 4.1), the stable nuclides fall along a monotonically increasing line called the stability line. The stability of the nucleus is determined by competing forces: the ‘strong force’ that binds the nucleons (protons and neutrons) together and the Coulomb force that repulses particles of like charge, e.g. protons. The interplay between the forces is illustrated in Fig. 4.3.

For best stability, the nucleus has an equal number of protons and neutrons. This is a quantum mechanic feature of bound particles and in Fig. 4.1 this is illustrated by a straight line. It is also seen that the stability line follows the straight line for the light elements but that there is considerable deviation (neutron excess) for the heavier elements. The explanation is the large Coulomb force in the heavy elements which have many protons in close proximity. By diluting the charge by non-charged neutrons, the distance between the charges increases and the Coulomb force decreases.

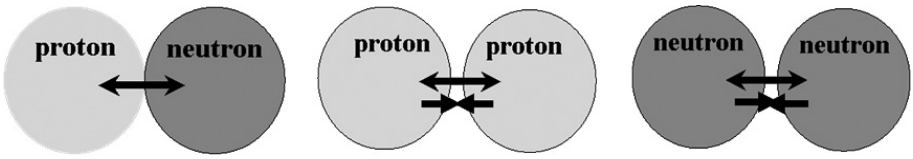


FIG. 4.3. Between the proton and a neutron, there is a nuclear force that amounts to 2.225 MeV. The nucleons form a stable combination called deuterium, an isotope of hydrogen. In a system of two protons, the nuclear force is equally strong to a neutron–proton, but the repulsive Coulomb forces are stronger. Thus, this system cannot exist. The nuclear force between two neutrons is equally strong and there is no Coulomb force. Nevertheless, this system cannot exist due to other repulsive forces, a consequence of the rules of pairing quarks.

4.1.3. Binding energy, Q-value, reaction threshold and nuclear reaction formalism

There are no barriers and no repulsive forces between a free proton and neutron, and they can fuse at low kinetic energies to form a deuterium nucleus, which has a weight somewhat smaller than the sum of the free neutron and proton weights. This mass difference can be converted into energy using Albert Einstein's formula $E = mc^2$ and is found to be 2.2 MeV. This is also the energy released as a γ photon in the reaction. To separate the two nucleons in the deuterium nucleus, at least 2.2 MeV have to be added. The energy gained or lost in a nuclear reaction is called the Q-value. In a somewhat more complex reaction, $^{14}N(p, \alpha)^{11}C$, the Q-value is calculated as the difference between the summation of the mass of the particles before the reaction (p, ^{14}N) from the mass of the particles after the reaction (α, ^{11}C). It should be noted that it is the mass of the nucleus and not the atomic mass that is used. Using a Q-value calculator[1], the Q-value for the reaction $^{14}N(p, \alpha)^{11}C$ is –2923.056 keV. This means that the proton, when it reaches the ^{14}N nucleus, has to have a kinetic energy of at least 2.93 MeV in order to make the reaction possible.

However, before it hits the nucleus, the proton has to overcome the barrier created by the repulsive Coulomb force between the proton and the positive ^{14}N nucleus. During the passage, the proton loses some energy and the starting value, called the threshold value, must then exceed the Q-value. The same calculator gives the threshold value of 3.14 MeV for the ^{11}C production reaction.

The reaction energy (the 'Q-value') is positive for exothermal reactions (spontaneous reactions) and negative for endothermal reactions. Since all radioactive decays are spontaneous, they need to have positive Q-values. Some reactions used

[1] For example, http://nucleardata.nuclear.lu.se/database/masses/

to produce radionuclides, mainly those that are based upon thermal neutrons, have positive Q-values but reactions based on positive particles usually have negative Q-values, e.g. extra energy needs to be added to get the reaction going.

4.1.4. Types of nuclear reaction, reaction channels and cross-section

As seen in Fig. 4.1, the radionuclides to the right of the stability line have an excess of neutrons compared to the stable elements and they are preferentially produced by irradiating a stable nuclide with neutrons. The radionuclides to the left are neutron deficient or have an excess of charge and, hence, they are mainly produced by irradiating stable elements by a charged particle, e.g. p or d. Although these are the main principles, there are exceptions.

Usually, the irradiating particles have a large kinetic energy that is transferred to the target nucleus to enable a nuclear reaction (the exception being thermal neutrons that can start a reaction by thermal diffusion). Figure 4.4 shows schematically an incoming beam incident upon the target, where it may be scattered and absorbed. It can transfer its energy totally or partly to the target nucleus and can interact with parts of or the whole of the target nucleus. Since the produced activity should be high, the target is also usually thick.

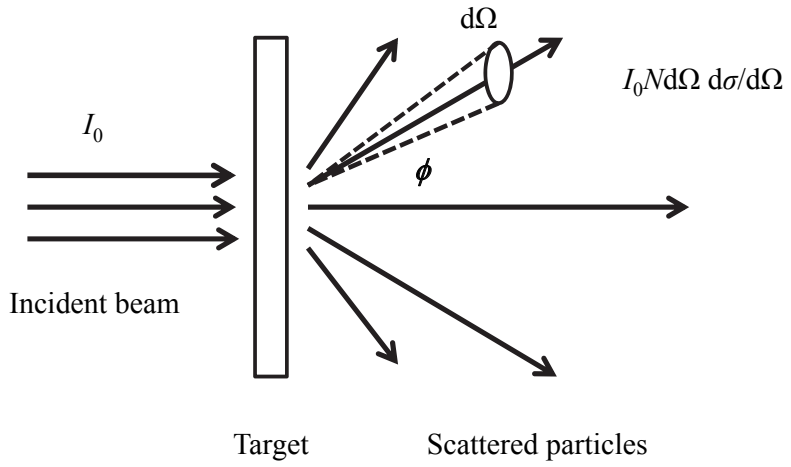


FIG. 4.4. Target irradiation. A nuclear physicist is usually interested in the particles coming out, their energy and angular distribution, but the radiochemist is mainly interested in the transformed nuclides in the target.

In radionuclide production, the nuclear reaction always involves a change in the number of protons or neutrons. Reactions that result in a change in the

number of protons are preferable because the product becomes a different element, facilitating chemical separation from the target, compared to an (n, γ) reaction, where the product and target are the same.

Neutrons can penetrate the target at down to thermal energies. Charged particles need to overcome the Coulomb barrier to penetrate the nucleus (Fig. 4.5).

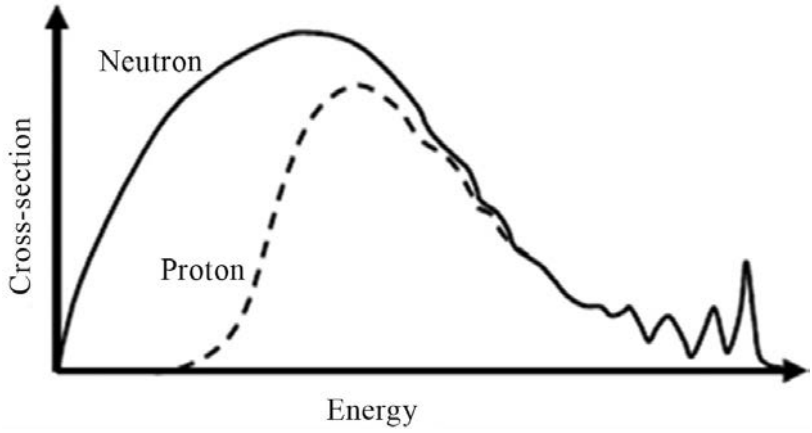


FIG. 4.5. General cross-sectional behaviour for nuclear reactions as a function of the incident particle energy. Since the proton has to overcome the Coulomb barrier, there is a threshold that is not present for the neutron. Even very low energy neutrons can penetrate into the nucleus to cause a nuclear reaction.

The parameter cross-section σ is the probability of a certain nuclear reaction happening and is expressed as a surface. It is the probability that a particle will interact per unit surface area of target. The geometrical cross-section of a uranium nucleus is roughly 10^{-28} m^2, and this area has also been taken to define the unit for cross-section barn (b). This is not an International System of Units unit but is commonly used to describe reaction probabilities in atomic and nuclear physics.

For fast particle reactions, the probability is usually less than the geometrical cross-section area of the nucleus, with probabilities in the range of millibarns. However, the probability of a hit is a combination of the area of both the nucleus and the incoming particle. The Heisenberg uncertainty principle states that the position and the momentum of particles cannot be simultaneously known to arbitrarily high precision. This implies that particles of well defined but low energy, such as thermal neutrons, will have a large uncertainty in their position. One may also say that they are increasing in size and nuclear reactions involving thermal neutrons may have very large cross-sections, sometimes of the order of several thousand barns.

The general equation for a nuclear reaction is:

$a + A \rightarrow b + B + Q$

where a is the incoming particle and A is the target nucleus in the ground state (the entrance channel). Depending on the energy and the particle involved, several nuclear reactions may happen, each with its own probability (cross-section). Each nuclear reaction creates an outgoing channel, where b is the outgoing particle or particles and B is the rest nucleus. *Q* is the reaction energy and can be both negative and positive.

A common notation of a nuclear reaction is A(a, b)B. If the incoming particle is absorbed, there is a capture process type (n, α) and in a reaction of type (p, n) charge exchange occurs. If many particles are expelled, the reaction can be referred to as (p, 3n). Each such reaction is called a reaction channel and is characterized by an energy threshold (an energy that makes the nuclear reaction possible, opens up the channel) and a probability (cross-section) varying with the incoming particle energy. A schematic illustration of different reaction channels opened in proton irradiation is given in Fig. 4.6.

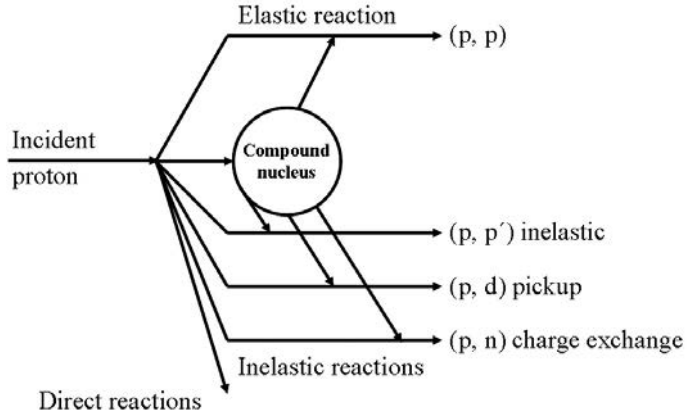


FIG. 4.6. A schematic figure showing some reaction channels upon proton irradiation.

Different reaction mechanisms can operate in the same reaction channel. Here, two ways are differentiated:

— The formation of a compound nucleus;
— Direct reactions.

The compound nucleus has a large probability to be formed in a central hit of the nucleus and is preferable at low energies close to the energy threshold of the reaction channel. Here, the incoming particle is absorbed and an excited compound nucleus formed. This compound nucleus will rapidly (~10^{-19} s) undergo decay (fragment) with the isotropic emission of neutrons and γ rays. Direct reactions preferentially occur at the edge of the nucleus or at high energies. The incoming energy is directly transferred to a nucleon (knock-on reaction) giving two outgoing particles. The outgoing particles usually have high energy and are emitted in about the same direction as the incoming particle.

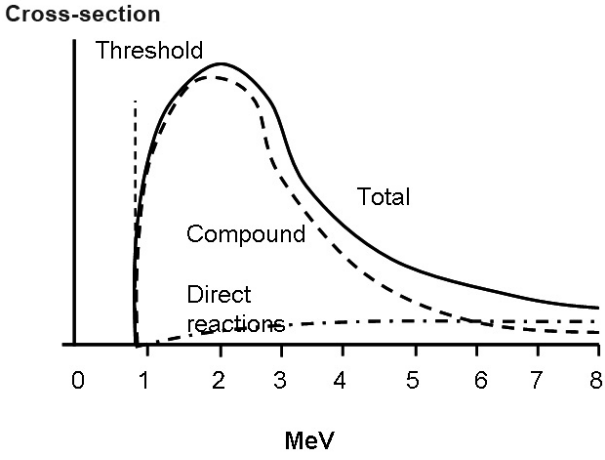


FIG. 4.7. A schematic view of particle energy variations of a cross-section for direct nuclear reactions and for forming a compound nucleus.

The production of radionuclides is due to a mixture of these two reaction types. Their probability varies with energy in different ways. The direct reactions are heavily associated with the geometrical size of the nucleus, and the cross-section is usually small and fairly constant with energy. The highest probability of forming a compound nucleus is just above the reaction threshold as seen in Fig. 4.7.

4.2. REACTOR PRODUCTION

There are two major ways to produce radionuclides: using reactors (neutrons) or particle accelerators (protons, deuterons, α particles or heavy ions). Since the target is a stable nuclide, either a neutron-rich radionuclide (reactor

produced) or a neutron deficient radionuclide (accelerator produced) is generally obtained.

4.2.1. Principle of operation and neutron spectrum

A nuclear reactor is a facility in which a fissile atomic nucleus such as ^{235}U, ^{239}Pu or ^{241}P absorbs a low energy neutron and undergoes nuclear fission. In the process, fast neutrons are produced with energies from about 10 MeV and below (the fission neutron spectrum). The neutrons are slowed down in a moderator (usually water) and the slowed down neutrons start new fissions. By regulating this nuclear chain reaction, there will be a steady state of neutron production with a typical neutron flux of the order of 10^{14} neutrons $\cdot$ $cm^{-2} \cdot s^{-1}$.

Since neutrons have no charge and are, thus, unaffected by the Coulomb barrier, even thermal neutrons (0.025 eV) can enter the target nucleus and cause a nuclear reaction. However, some nuclear reactions, depending upon the cross-section, require fast neutrons (energy < 10 MeV).

A reactor produces a neutron cloud in which the target is placed so that it will be isotropically irradiated. Placing the target in different positions exposes it to neutrons of different energy. Usually, the reactor facility has a pneumatic system for placing targets at predefined positions. One has to consider the heat that is generated in the reactor core, since the temperature at some irradiation positions may easily reach 200°C. The reactor is characterized by the energy spectrum, the flux (neutrons $\cdot$ $cm^{-2} \cdot s^{-1}$) and the temperature at the irradiation position.

Most reactors in the world are for energy production and, for safety reasons, cannot be used for radionuclide production. Usually, only national research reactors are flexible enough for use in radioisotope production.

4.2.2. Thermal and fast neutron reactions

The most typical neutron reaction is the (n, γ) reaction in which a thermal neutron is captured by the target nucleus forming a compound nucleus. The decay energy is emitted as a prompt γ ray. A typical example is the reaction $^{59}Co(n, \gamma)^{60}Co$ that produces an important radionuclide used in external therapy. However, since the produced radionuclide is of the same element as the target, the specific activity *a*, i.e. the radioactivity per mass of the sample, is low. This type of nuclear reaction is of little interest when labelling radiopharmaceuticals. In light elements, other nuclear reactions resulting from thermal neutron irradiation are possible, such as (n, p). Table 4.1 lists possible production reactions for some biologically important radionuclides.

TABLE 4.1. TYPICAL NUCLEAR REACTIONS IN A REACTOR FOR RADIONUCLIDE PRODUCTION

Type of neutrons	Nuclear reaction	Half-life $T_{1/2}$	Cross-section σ (mb)
Thermal	$^{59}Co(n, \gamma)^{60}Co$	5.3 a	2000
	$^{14}N(n, p)^{14}C$	5730 a	1.75
	$^{33}S(n, p)^{33}P$	25 d	0.015
	$^{35}Cl(n, \alpha)^{32}P$	24 d	0.05
Fast	$^{24}Mg(n, p)^{24}Na$	15 h	1.2
	$^{35}Cl(n, \alpha)^{32}P$	14 d	6.1

Nuclear reactions with thermal neutrons are attractive for many reasons. The yields are high due to large cross-sections and the high thermal neutron fluxes available in the reactor. In some cases, the yields are sufficiently high to use these reactions as the source of charged secondary particles, e.g. $^{6}Li(n, \alpha)^{3}H$ for the production of high energy ^{3}H ions, which can then be used for the production of ^{18}F by $^{16}O(^{3}H, n)^{18}F$. The target used is $^{6}LiOH$, in which the produced ^{3}H ions will be in close contact with the target ^{16}O. A drawback of this production is that when the target is dissolved the solution is heavily contaminated with ^{3}H water that might be difficult to remove. Today, with an increasing number of hospital based accelerators, there is little need of neutron produced ^{18}F.

Another reactor produced neutron deficient radionuclide is ^{125}I:

$$^{124}Xe(n, \gamma)^{125}Xe\ (T_{1/2} = 17\ h) \rightarrow {}^{125}I\ (T_{1/2} = 60\ d)$$

This is currently the common way of producing high quality ^{125}I. A drawback is that ^{124}Xe has a natural abundance of 0.1%. To increase the production yield, one needs to work with expensive enriched targets. However, these can be reused several times. This is an example of a generator system where the mother is shorter lived than the daughter. Although there is no need to make a separation between the mother and daughter, the target, after irradiation, has to be stored for some days to allow the decay of ^{125}Xe to be complete. The expensive target gas ^{124}Xe is carefully removed and the ^{125}I is washed out from the walls of the target capsule.

Many reactor produced radionuclides emit high energy β particles that contribute to the absorbed dose (but not the imaging signal) to patients, which is a drawback in diagnostic procedures. However, a few β emitting isotopes result in daughter nuclei that emit γ rays with long de-excitation times (metastable

excited levels), instead of the more common prompt (10^{-14} s) γ emission. Such radioisotopes are suitable for nuclear medicine imaging, since they principally yield γ radiation, with some electron emission, a consequence of internal conversion. The most commonly used radionuclide in nuclear medicine, ^{99m}Tc, is of this type. The 'm' after the atomic mass signifies that this is the metastable version of the radionuclide.

In radionuclide therapy, in contrast to diagnostic applications, the emission of high energy β radiation is desirable. Most radionuclides for radiotherapy are, therefore, reactor produced. Examples include ^{90}Y, ^{131}I and ^{177}Lu. A case of interest to study is ^{177}Lu, which can be produced in two different ways using thermal neutrons. The most common production route is still the (n, γ) reaction on ^{176}Lu, which opposes two conventional wisdoms in practical radionuclide production for biomolecular labelling:

(a) Not to use a production that yields the same product element as the target since it will negatively affect the labelling ability due to the low specific radioactivity;
(b) Not to use a target that is radioactive.

However, ^{176}Lu is a natural radioactive isotope of lutetium with an abundance of 2.59%. Figure 4.8 shows how ^{177}Lu needs to be separated from the dominant ^{175}Lu to decrease the mass of the final product. This method of production works because the high cross-section (2020 b) of ^{176}Lu results in a high fraction of the target atoms being converted to ^{177}Lu, yielding an acceptable specific radioactivity of the final product.

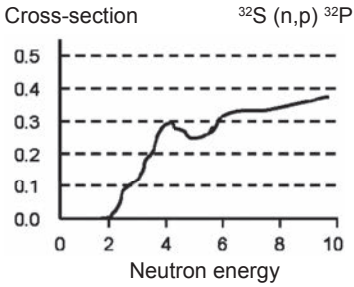
On the right of Fig. 4.8, an indirect way to produce ^{177}Lu from ^{176}Yb is also shown. This method of production utilizes a generator nuclide ^{177}Yb, produced by an (n, γ) reaction, which then decays to ^{177}Lu. In principle, by chemically separating lutetium from ytterbium, one would obtain the highest possible specific radioactivity. However, the chemical separation between two lanthanides is not trivial and, thus, it is difficult to obtain ^{177}Lu without substantial contamination of the target material Yb that may compete in the labelling procedure. Furthermore, the cross-section for this reaction is almost a thousandfold lower, resulting in a much lower product yield.

Reactions involving fast neutrons usually have cross-sections that are of the order of millibarns, which, coupled with the much lower neutron flux at higher energy relative to thermal neutron fluxes, leads to lower yields. However, there are some important radionuclides, e.g. ^{32}P that have to be produced this way. Figure 4.9 gives the details of this production.

	^{175}Lu	^{176}Lu	^{177}Lu	^{178}Lu
$T_{1/2}$	Stable	3.78 10^{10} a	6.734 d	28.4 min
Abundance (%)	97.41	2.59		
σ (mb)		2020		

	^{175}Lu	^{176}Lu	^{177}Lu	^{178}Lu
$T_{1/2}$	Stable	3.78 10^{10} a	6.734 d	28.4 min
Abundance (%)	97.41	2.59		
σ (mb)		2020		
	^{174}Yb	^{175}Yb	^{176}Yb	^{177}Yb
$T_{1/2}$	Stable	4.185 d	Stable	1.911 h
Abundance (%)	31.8		12.7	31.8
σ (mb)			2.85	

FIG. 4.8. Production of ^{177}Lu from ^{176}Lu (left) and from ^{176}Yb (right).



	^{32}S	^{33}S	^{34}S
$T_{1/2}$	Stable	Stable	Stable
Abundance (%)	95.02	0.75	4.21
σ (mb)	varying	varying	varying
	^{31}P	^{32}P	^{33}P
$T_{1/2}$	Stable	14.26 d	25.4 d
Abundance (%)	100		
σ (mb)			

FIG. 4.9. Data for the production of ^{32}P in the nuclear reaction ^{32}S(n, p)^{32}P. The reaction threshold is 0.51 MeV. From the cross-section data, it can be seen that there is no substantial yield until an energy of about 2 MeV. The yield is an integration of the cross-section data and the neutron energy spectrum. A practical cross-section can be calculated to about 60 mb.

4.2.3. Nuclear fission, fission products

Uranium-235 is not only used as fuel in a nuclear reactor but it can also be used as a target to produce radionuclides. Uranium-235 irradiated with thermal neutrons undergoes fission with a cross-section of 586 b. The fission process results in the production of two fragments of ^{235}U nucleus plus a number of free neutrons. The sum of the fragments' mass will be close to the mass of ^{235}U, but they will vary according to Fig. 4.10.

The masses of the ^{99}Mo and ^{134}Sn produced in the reaction:

$$^{235}\text{U} + \text{n} \rightarrow {}^{236}\text{U} \rightarrow {}^{99}\text{Mo} + {}^{134}\text{Sn} + 3\text{n}$$

are marked in Fig. 4.10. Some medically important radionuclides are produced by fission, such as ^{90}Y (therapy) and ^{99m}Tc (diagnostic). They are not produced directly but by a generator system:

$$^{90}\text{Sr}\ (28.5\ \text{a}) \rightarrow {}^{90}\text{Y}\ (2.3\ \text{d}) \text{ and } {}^{99}\text{Mo}\ (2.7\ \text{d}) \rightarrow {}^{99\text{m}}\text{Tc}\ (6\ \text{h})$$

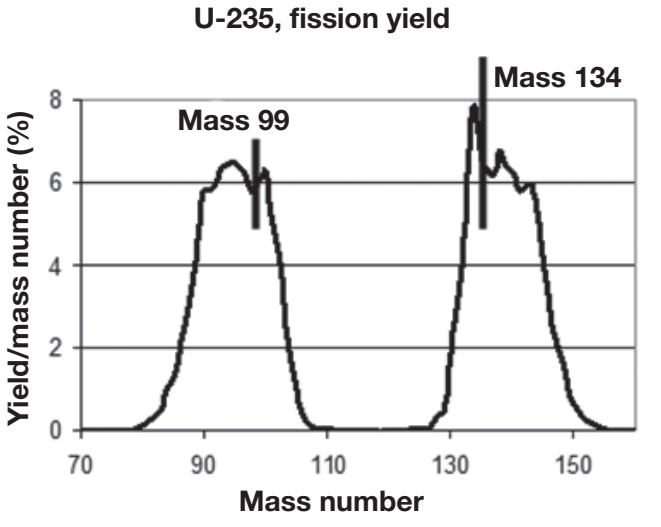


FIG. 4.10. The yield of fission fragments as a function of mass.

The primary radionuclides produced are then ^{90}Sr and ^{99}Mo, or more precisely the mass numbers 90 and 99.

Another important fission produced radionuclide in nuclear medicine, both for diagnostics and therapy, is ^{131}I. The practical fission cross-section for this production is the fission cross-section of ^{235}U multiplied by the fraction of fragments having a mass of 131 or 586 × 0.029 = 17 b. The probability of producing a mass of 131 is 2.9% per fission. Iodine-131 is the only radionuclide with a mass of 131 that has a half-life of more than 1 h, meaning that all of the others will soon have decayed to ^{131}I.

4.3. ACCELERATOR PRODUCTION

Charged particles, unlike neutrons, are unable to diffuse into the nucleus, but need to have sufficient kinetic energy to overcome the Coulomb barrier. However, charged particles are readily accelerated to kinetic energies that open up more reaction channels than fast neutrons in a reactor. An example is seen in Fig. 4.11 that also illustrates alternative opportunities with: p, d, ^{3}He and ^{4}He or α, to produce practical and economic nuclear reactions.

$^{127}I(p, 5n)^{123}Xe \rightarrow {}^{123}I$

$^{124}Xe(p, np)^{123}Xe \rightarrow {}^{123}I$

$^{123}Te(p, n)^{123}I$

$^{122}Te(d, n)^{123}I$

$^{124}Te(p, 2n)^{123}I$

$^{121}Sb(^{4}He, 2n)^{123}I$

$^{121}Sb(^{3}He, n)^{123}I$

$^{123}Sb(^{3}He, 3n)^{123}I$

FIG. 4.11. Various nuclear reactions that produce ^{123}I. All of the reactions have been tried and can be performed at relatively low particle energies. The ^{123}Xe produced in the first two reactions decays to ^{123}I with a half-life of about 2 h. In the first reaction, the ^{123}Xe is separated from the target and then decays, while in the second reaction, the ^{123}I is washed out of the target after decay.

An accelerator in particle physics can be huge, as in the European Organization for Nuclear Research (CERN), with a diameter of more than 4 km. Accelerators for radionuclide production are much smaller, as they need to accelerate particles to much lower energies. The first reaction in Fig. 4.11, where five neutrons are expelled, is the most energy demanding, as it requires a proton energy of about 5 × 10 MeV = 50 MeV (the rule of thumb is that about 10 MeV are required per expelled particle). All of the other reactions require 20 MeV or less (see Table 4.2).

Another advantage with accelerator production is that it is usually easy to find a nuclear reaction where the product is a different element from the target. Since different elements can be separated chemically, the product can usually be of high specific radioactivity, which is important when labelling biomolecules.

A technical difference between reactor and accelerator irradiation is that in the reactor the particles come from all directions but in the accelerator the particles have a particular direction. The number of charged particles is often smaller and is usually measured as an electric current in microamperes (1 μA = 6×10^{12} protons/s but 3×10^{12} alpha/s because of the two charges of the α particle).

TABLE 4.2. CHARACTERIZATION OF ACCELERATORS FOR RADIONUCLIDE PRODUCTION

Proton energy (MeV)	Accelerated particles	Used for
<10	Mainly single particle, p or d	PET
10–20	Usually p and d	PET
30–40	p and d, ^{3}He and ^{4}He may be available	PET, commercial production
40–500	Usually p only	Often placed in national centres and have several users

A drawback in accelerator production is that charged particles are stopped more efficiently than neutrons; for example, 16 MeV protons are stopped in 0.6 mm Cu. A typical production beam current of 100 μA hitting a typical target area of 2 cm^2 will then put 1.6 kW in a volume of 0.1 cm^3, which will evaporate most materials if not efficiently cooled. In addition, the acceleration of the beam occurs in a vacuum but the target irradiation is at atmospheric pressure or in gas targets at 10–20 times over pressure. To separate the vacuum from the target, the beam has to penetrate foils that will absorb some particle energy and they will also become strongly activated.

4.3.1. Cyclotron, principle of operation, negative and positive ions

There are several types of accelerator, all of which can, in principle, be used for radionuclide production. The dominant one for radionuclide production is currently the cyclotron that was invented by Lawrence in the early 1930s. Cyclotrons were first installed in hospitals in the 1960s, but during the past two decades, hospital based small cyclotrons yielding 10–20 MeV protons have become fairly common, especially with the rise of PET.

A cyclotron is composed of four systems:

(a) A resistive magnet that can create a magnetic field of 1–2 T;
(b) A vacuum system down to 10^{-5} Pa;
(c) A high frequency system (about 40 MHz) providing a voltage with a peak value of about 40 kV, although these figures can vary considerably for different systems;
(d) An ion source that can ionize hydrogen to create free protons as well as deuterium and α particles.

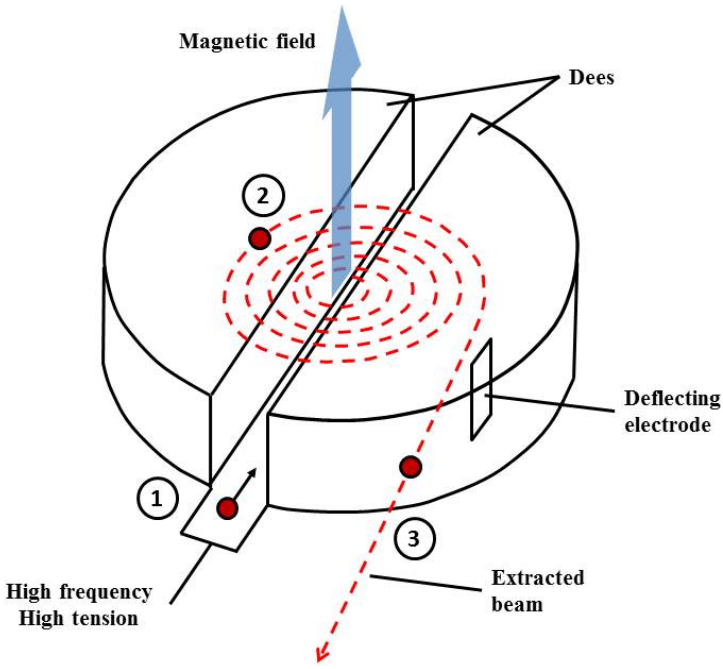


FIG. 4.12. The cyclotron principle. A negative ion is injected into the gap between D-shaped magnets (Dees) (1). An alternating electric field is applied across the gap, which causes the charge to accelerate. The magnetic force on a moving charge forces it to bend into a semicircular path of ever increasing radius (2). The applied electric field is reversed in direction each time the charged particle reaches the gap, so that it is continuously accelerated, until finally being ejected (3).

The inside of a cyclotron is shown in Fig. 4.12. The ion source is usually placed inside the vacuum and in the centre (internal), but, in larger machines, can be external. The ions are then injected from the outside through a central hole in the magnet. The main idea of the ion source is to have a slow flow of gas that is made into plasma by an arc discharge. The desired ion species are extracted through a collimator and accelerated in a static electric field. There are several types of ion source with different operating characteristics. In modern accelerators, negative ions, protons or deuterium with two orbit electrons are usually used. These facilitate extraction of the beam.

The ions leave the ion source with some velocity. Since the vacuum chamber is in a magnetic field, the ions move in a circular orbit. Inside the vacuum chamber, there are two electrodes, historically called the 'Dees' since the first ones have the shape of the letter D. These electrodes are hollow, which enables the ions to move freely inside the electrodes. There is a gap between

the electrodes called the acceleration gap. If a voltage is applied between the electrodes, the ions will experience the potential gradient when traversing the gap between the electrodes. If the voltage polarity is switched at the correct rate, the ions will be continuously accelerated when crossing the gap, thus resulting in an increase in the ions' energy and velocity. As their velocity increases, the ions will move into a circular orbit of increasing radius. The time taken for the ions to return to the gap is independent of their radius in accelerators <30 MeV. For the cyclotron to operate correctly, it is necessary for the frequency of the electric field across the Dees to be the same as the frequency of the circulating ions, so that the polarity changes upon each traversal of the ions across the Dees.

In commercial accelerators, with high beam currents of several milliamperes, it is usual to have an internal target for radionuclide production located inside the chamber. In accelerators with lower beam currents <100 μA, such as those dedicated for PET hospital facilities, it is more common to extract the beam onto an external target system. The modes of extraction depend upon whether positive or negative ions are accelerated. Extraction of positive ions is made by using a deflector that applies a static electric field which acts upon the particles when in the outer orbits. Some beam current is invariably lost in the process and the deflector often becomes quite radioactive.

Modern proton/deuterium accelerators usually accelerate negative ions that are more easily extracted. In these systems, a thin carbon foil is used that will strip away the two orbit electrons. As a consequence, the particles suddenly change from negative to positive charge and are effectively bent out of the magnetic field with an almost 100% extraction efficiency and with little activation.

The extracted beam can either be transported further in a beam optical transport system or will hit a production target directly. The target is usually separated from the vacuum by metallic foils that are strong enough to withstand the pressure difference and the heat from the beam energy, as it is transferred and absorbed by the foils. The reason why two foils are used is that the heat produced by the beam passage has to be removed, which is facilitated by a flow of helium gas between the foils. Helium is preferred as the cooling medium since no induced activity will be produced in this gas.

4.3.2. Commercial production (low and high energy)

If the proton energy is >30 MeV, the particles tend to be relativistic, i.e. their mass and their cycle time in orbit increase. A constant frequency of the accelerating electric field would cause the ions to come out of phase. This can be compensated for either by increasing the magnetic field as a function of the cyclotron radius (isochronic cyclotrons) or by decreasing the radiofrequency

during acceleration (synchrocyclotrons). Such accelerators tend to be more complex and expensive and, for this reason, 30 MeV is a typical energy for commercial accelerators that need to have large beam currents and to be both reliable and cost effective.

Commercial accelerators usually run beam currents of several milliamperes. Since it is technically difficult to extract such high beam currents due to heating problems in the separating foils, most commercial accelerators use internal targets, i.e. targets that are placed inside the cyclotron vacuum as shown schematically in Fig. 4.13.

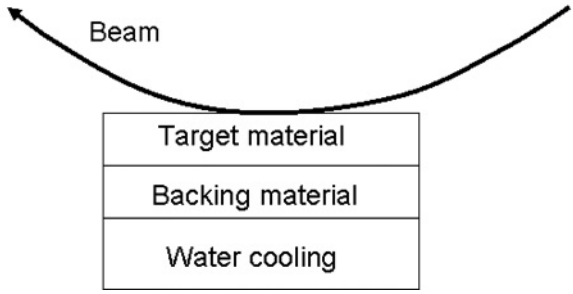


FIG. 4.13. Schematic image of an internal target. The target material is usually thin (a few tenths of a micrometre) and evaporated on a thicker backing plate. The target ensemble is water cooled on the back. An advantage is that the beam is spread out over a large area which facilitates cooling.

Many patients in nuclear medicine undergo single photon emission computed tomography (SPECT) investigations. Besides reactor produced ^{99m}Tc, commercial cyclotrons commonly produce ^{67}Ga, ^{111}In, ^{123}I and ^{201}Tl. In addition, some PET radionuclides, such as ^{124}I, are becoming commercially available. Increasing demand for the ^{68}Ge/^{68}Ga generator has also led to commercial production of the cyclotron produced mother nuclide ^{68}Ge. Only a few radionuclides of medical interest require production energies above 30 MeV. A limited number of high energy accelerators with high beam currents, usually at national physics laboratories, have the capacity for the production of, for example, ^{52}Fe and ^{61}Cu and other isotopes used for research activities.

4.3.3. In-house low energy production (PET)

Commercial accelerators dedicated to PET radioisotope production are limited both in energy (<20 MeV) and in beam current (<100 μA). Many production routes utilize gases or water as target materials and, therefore, external

targets are to be preferred. Owing to the relatively low beam current, extraction is not a problem. Since internal targets need to be taken in and out of the cyclotron vacuum, they are not usually implemented in PET cyclotrons.

The importance of choosing the right reaction and target material is crucial and is illustrated by the production of ^{18}F. There are several nuclear reactions that can be applied (Table 4.3).

TABLE 4.3. DIFFERENT NUCLEAR REACTIONS FOR THE PRODUCTION OF ^{18}F

$^{20}Ne(d, \alpha)^{18}F$	The nascent ^{16}F will be highly reactive. In the noble gas Ne, it will diffuse and stick to the target walls; difficult to extract
$^{21}Ne(p, \alpha)^{18}F$	Same as above; in addition, the abundance of ^{21}Ne is low (0.27%) and needs enrichment
$^{19}F(p, d)^{18}F$	The product and target are the same element; poor specific radioactivity
$^{16}O(\alpha, d)^{18}F$	Cheap target but accelerators that can accelerate α particles to 35 MeV are expensive and not common
$^{16}O(d, \gamma)^{18}F$	Small cross-section and no practical yields can be obtained
$^{18}O(p, n)^{18}F$	Expensive enriched target material but the proton energy is low (low cost accelerator), which makes this the nuclear reaction of choice

Not only the nuclear reaction is important, but also the chemical composition of the target. To irradiate ^{18}O as a gas would be the purest target (only target nuclide present) but handling a highly enriched gas in addition to the hot-atom chemistry is complicated. Still, for some applications, this might be the best choice. To irradiate ^{18}O as an oxide and a solid target is possible but the process following irradiation to dissolve the target and to chemically separate ^{18}F is complex, has a low yield and other elements in the oxide could potentially contribute unwanted radioactivity. Enriched ^{18}O water is a target of choice as ^{18}O is the dominant nucleus and hydrogen does not contribute to any unwanted radioactivity. There is usually no need for target separation as water containing ^{18}F can often be directly used in the labelling chemistry. The target water can also, after being diluted with saline, be injected directly into patients, e.g. ^{18}F-fluoride for PET bone scans. Water targets will produce ^{18}F-fluoride for use in stereospecific nucleophilic substitutions. An alternative production route is neon gas production, $^{20}Ne(d, \alpha)^{18}F$. Adding $^{19}F_2$ gas to the neon as a carrier yields $^{18}F^{19}F$ that can be used for electrophilic substitution. Adding carrier lowers the specific radioactivity of the labelled product.

A problem is the heat generated when the beam is stopped in a few millilitres of target water. High pressure targets that force the water to remain in the liquid phase can overcome some of these problems but production is usually limited to beam currents <40 μA. Gas and solid targets are advantageous as they can withstand higher beam currents.

There are also several options for the production of ^{11}C. These include: $^{10}B(d, n)^{11}C$, $^{11}B(p, n)^{11}C$ and $^{14}N(p, \alpha)^{11}C$. The reactions on boron are made as solid target irradiations while the reaction on nitrogen is a gas target application.

The routine production routes of common positron emitters associated with PET are summarized in Table 4.4.

TABLE 4.4. COMMONLY USED RADIONUCLIDES IN PET

Radionuclide	Nuclear reaction	Yield (GBq)
^{15}O	$^{14}N(d, n)^{15}O$ gas target	15
^{13}N	$^{16}O(p, \alpha)^{13}N$ liquid target	5
^{11}C	$^{14}N(p, \alpha)^{11}C$ gas target	40
^{18}F	$^{18}O(p, n)^{18}F$ liquid target	100

Oxygen-15 is produced by deuteron bombardment of natural nitrogen through the $^{14}N(d, n)^{15}O$ nuclear reaction. An alternative is the $^{15}N(p, n)^{15}O$ reaction if a deuterium beam is not available. In this case, the target needs to be enriched. In the nitrogen target, ^{15}O-labelled molecular oxygen is produced directly. Direct production of ^{11}C-labelled carbon dioxide is possible by mixing the target gas with 5% natural carbon dioxide as a carrier. Water labelled with ^{15}O is preferably made by processing ^{15}O-labelled molecular oxygen.

Carbon-11 is produced by proton bombardment of natural nitrogen. By adding a small amount of oxygen to the target gas (<0.5%), carbon dioxide ($^{11}CO_2$) will be produced. Adding 5% hydrogen to the target will produce methane ($^{11}CH_4$).

Liquid targets are today by far the most popular and widely used for the production of ^{13}N. The reaction of protons on natural water produces nitrate and nitrite ions, which can be converted to ammonia by reduction. Water targets can also be used to form ammonia directly with the addition of a reducing agent, e.g. ethanol or hydrogen.

4.3.4. Targetry, optimizing the production regarding yield and impurities, yield calculations

When the nucleus is hit by an energetic particle, a complex interplay between physical and statistical laws determines the result. Important parameters are the entrance particle energy, the target thickness and the reaction channel cross-sections for the particle energies in the target. Computer codes such as ALICE and TALYS are available to calculate the size and the energy dependence of the cross-section for a certain reaction channel but they are not easy to apply; hence, caution should be exercised when interpreting the results from such codes. However, a rough estimation of the irradiating particle energy can be obtained using a well known rule of thumb in radionuclide production (illustrated in Fig. 4.14).

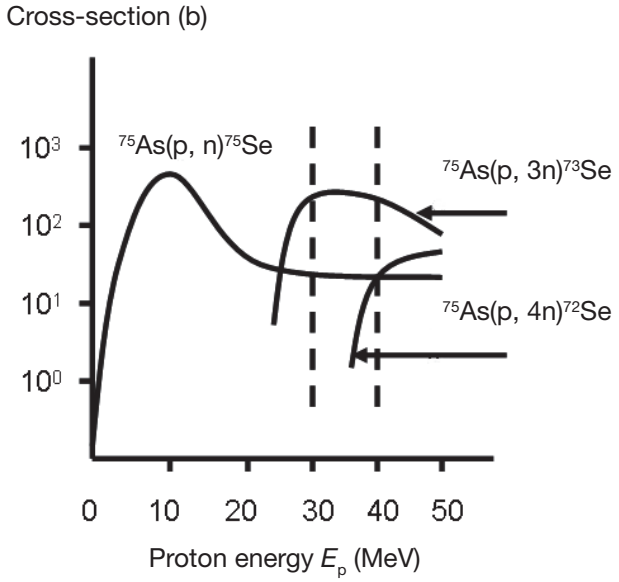


FIG. 4.14. Excitation functions of $^{75}As(p, xn)^{72,73,75}Se$ reactions. The optimal energy for the production of ^{73}Se is to use a proton energy of 40 MeV that is degraded to 30 MeV in the target.

The maximum cross-sections are found at about 10, 30 and 40 MeV for the (p, n), (p, 3n) and (p, 4n) reactions, respectively. Thus, it takes about 10 MeV to expel a nucleon, i.e. a proton of 50 MeV can cover radionuclide productions that involve the emission of about five nucleons. At low energy, there is a disturbing production of ^{75}Se and if excessively high proton energy is used, another

unwanted radionuclide impurity is produced, namely ^{72}Se. The latter impurity can be avoided completely by restricting the proton energy to an energy lower than the threshold for the (p, 4n) reaction. The impurity that results from the (p, n) reaction cannot be avoided but can be minimized by using a target thickness that avoids the lower proton energies (having the highest (p, n) cross-sections).

Figure 4.14 highlights the fact that the chosen production parameters are a compromise. A proton range of 40–30 MeV uses the (p, 3n) cross-section well. Some ^{72}Se contamination is acceptable in order to increase the yield of ^{73}Se. An important factor is the half-life of ^{75}Se ($T_{1/2}$ = 120 d), ^{73}Se ($T_{1/2}$ = 7.1 h) and ^{72}Se ($T_{1/2}$ = 8.5 d). Sometimes, it is possible to wait for the decay of the radioactive contaminants. Although not the case here, sometimes a long half-life contaminant is not a serious disadvantage. If the product half-life is long, then there may be little product decay over the target irradiation time compared to short lived radionuclides.

The practical set-up when undertaking radionuclide production is as follows. A suitable As target is made and irradiated with 40 MeV protons. The thickness of the target is such that it decreases the proton energy to 30 MeV. This then gives a radioactivity yield of the desired radionuclide at the end of bombardment, which is mainly dependent upon the beam current and the irradiation time. The yield is usually expressed in gigabecquerels per microampere hours (GBq/μA · h), i.e. the produced radioactivity per time integrated beam current. If possible, it is endeavoured to keep the radioactivity of the contaminants at low levels (<1%). However, from the end of bombardment, the ratio of the product relative to any long lived radio-contaminants begins to decrease.

4.4. RADIONUCLIDE GENERATORS

Whenever a radionuclide (parent) decays to another radioactive nuclide (daughter), this is called a radionuclide generator. Most natural radioactivity is produced in generator systems starting with uranium isotopes and ^{232}Th, and involves about fifty radioactive daughters. Several radionuclides used in nuclear medicine are produced by generator systems such as the ^{99}Mo production of ^{99m}Tc, which subsequently decays to ^{99}Tc. The extremely long half-life of ^{99}Tc ($T_{1/2}$ = 2.1 × 10^5 a) means that ^{99m}Tc can be safely used as a clinical isotope without any radiological concerns. In other nuclides, the creation of a radioactive nuclide may be more important, e.g. the positron emitter ^{52}Fe ($T_{1/2}$ = 8 h) decays to ^{52}Mn ($T_{1/2}$ = 21 min) which is also a positron emitter. Furthermore, radionuclides used in therapy may themselves be generators such as ^{211}At ($T_{1/2}$ = 7 h) decaying to ^{211}Po ($T_{1/2}$ = 0.5 s) or ^{223}Ra, which generates a series of relatively short lived radioactive daughters in situ.

When talking about generators in nuclear medicine, a special case is usually considered in which a long lived mother generates a short lived daughter, which after labelling is administrated to the patient. Generally, this is a practical way to deliver short lived radionuclides to hospitals which otherwise, for logistical reasons, would not have been possible. The half-life should be sufficiently long so that the radionuclide can be delivered to hospitals, and provide the radioactive product for a number of patients over days or weeks. A typical example is the $^{99}Mo/^{99m}Tc$ generator (Fig. 4.15), which produces the most used radionuclide in nuclear medicine. The half-life of the parent (2.7 d) is adequate for transport and delivery, and the daughter has a suitable half-life (6 h) for patient investigations. The generator is used for about two to three half-lives of the parent (1 week) after which time it is renewed.

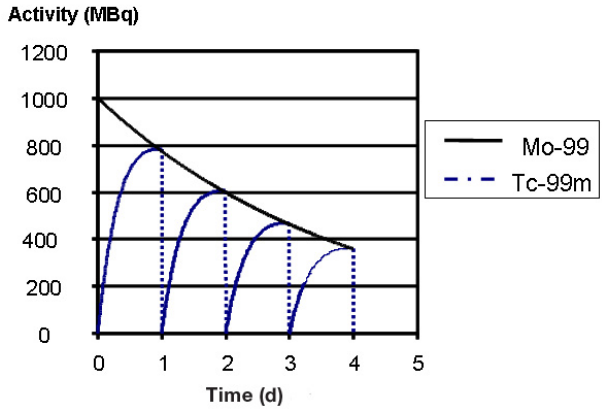


FIG. 4.15. Elution of a $^{99}Mo/^{99m}Tc$ generator. The generator has a nominal activity of 1000 MBq on day 0 (Monday). It is eluted daily, five times a week, yielding 1000, 780, 600, 470 and 360 MBq.

4.4.1. Principles of generators

Generator systems require that the parent is a reactor or accelerator produced by the methods described above and that the daughter radionuclide of interest can easily be separated from the parent. The $^{99}Mo/^{99m}Tc$ generator exhibits these characteristics. Most commercial generators use column chromatography, in which ^{99}Mo is adsorbed onto alumina. Eluting the immobilized ^{99}Mo on the column with physiological saline elutes the soluble ^{99m}Tc in a few millilitres of

liquid. In fact, most generators in nuclear medicine use ion exchange columns in much the same way due to its simplicity of handling.

In generator systems, the daughter radionuclide is formed at the rate at which the parent decays, $\lambda_P \times N_P$. It also decays at the same rate, $\lambda_D \times N_D$, as the parent, once a state of transient equilibrium has been reached. The equations that describe the relationship between parent and daughter are provided in Chapter 1.

Another generator of increasing importance is ^{68}Ge, which has a half-life of 271 d that produces a short lived positron emitter ^{68}Ga ($T_{1/2}$ = 68 min). This is produced as a +3 ion that can be tagged, using a chelating agent such as DOTA, to small peptides, e.g. ^{68}Ga-DOTATOC. Owing to the long half-life of the mother, the generator can be operated for up to two years and can be eluted every 5 h. One problem with such a long lived generator is keeping it sterile, and furthermore, the ion exchange material is exposed to high radiation doses that may reduce the elution efficiency and the quality of the product.

The ^{90}Sr/^{90}Y generator is used to produce the therapeutic radionuclide ^{90}Y. This generator is not distributed to hospitals but is operated in special laboratories on account of radiation protection considerations associated with the long lived parent. The daughter, ^{90}Y, has a half-life of 2.3 d which is adequate for transport of the eluted ^{90}Y to distant hospitals.

^{81}Rb (4.5 h)/^{81m}Kr (13.5 s) for ventilation studies and ^{82}Sr (25.5 d)/^{82}Rb (75 s) for cardiac PET studies are examples of other generators with special requirements due to the extremely short half-life of the eluted product. Recently, generator systems producing α emitters for therapy have become available, e.g. ^{225}Ac (10 d)/^{213}Bi (45.6 min).

4.5. RADIOCHEMISTRY OF IRRADIATED TARGETS

During target irradiation, a few atoms of the wanted radionuclide are produced within the bulk target material. The energy released in a nuclear reaction is large relative to the electron binding energies and the radionuclide is, therefore, usually ‘born’ almost naked with no or few orbit electrons. This ‘hot atom’ will undergo chemical reactions depending on the target composition. In a gas or liquid target, these hot atom reactions may even cause the activity to be lost in covalent bonds to the target holder material. During irradiation, the target is also heated and its structure and composition may change. A pressed powder target may be sintered and become more ceramic, which makes it more difficult to dissolve. The target may melt and the radioactivity may diffuse in the target and even possibly evaporate. In designing a separation method, all of these factors have to be considered. Fast, efficient and safe methods are required to

separate the few picograms of radioactive product from the bulk target material which is present in gram quantities.

Separation of the radionuclide already starts in the target as demonstrated in the production of $^{11}CO_2$. Carbon-11 is produced in a (p, α) reaction on nitrogen gas. To enable the production of CO_2, some trace amounts of oxygen gas (0.1–0.5%) are added. However, at low beam currents, mainly CO will be formed, since the target will not be heated. At high beam currents, the CO will be oxidized to the chemical form CO_2. The separation, made by letting the target through a liquid nitrogen trap, is simple and efficient. By adding hydrogen gas instead, the product will be CH_4.

The skill in hot-atom chemistry is to obtain a suitable chemical form of the radioactive product, especially when working with gas and liquid targets. Solid targets are usually dissolved and chemically processed to obtain the wanted chemical form for separation.

4.5.1. Carrier-free, carrier-added systems

The concept of specific activity *a*, i.e. the activity per mass of a preparation, is essential in radiopharmacy. If 100% of the product contains radioactive atoms, often called the theoretical *a*, then the relationship between the activity $\mathcal{A}$ in becquerels and the number of radioactive atoms *N* is given by $N = \mathcal{A}/\lambda$, where λ is the decay constant (1/s). The decay constant can be calculated from the half-life $T_{1/2}$ in seconds as $\lambda = \ln(2)/T_{1/2}$.

The specific activity *a* expressed as activity per number of radioactive atoms is then $\mathcal{A}/N = \lambda = \ln(2)/T_{1/2}$. For a short lived radionuclide, *a* will be relatively large compared to a long lived isotope. For example, *a* for ^{11}C ($T_{1/2}$ = 20 min) is 1.5×10^8 times larger than for ^{14}C ($T_{1/2}$ = 5730 a).

The specific activity *a* expressed in this way is a theoretical value that is rarely obtained in practical work. When producing ^{11}C, the target gas and target holder will contain stable carbon that will dilute the radioactive carbon as well as compete in the labelling process afterwards. A more empirical way to define *a* is to divide the activity by the total mass of the element under consideration. This value for ^{11}C will usually be a few thousand times lower than the theoretical value, while the production of ^{14}C can come closer to the theoretical *a*.

In the labelling process, *a* is usually expressed as the activity per number of molecules (a sum of labelled and unlabelled molecules). Instead of using the number of atoms or molecules, it is common to use the mole concept by dividing *N* by Avogadro's number ($N_A = 6.022 \times 10^{23}$). A common unit for *a* is then gigabecquerels per micromole.

If the radioactive atoms are produced and separated from the target without any stable isotopes, the process is said to be 'carrier-free'. If stable isotopes are

introduced as being a contaminant in the target or in the separation procedure, the process is said to have 'no carrier added', i.e. no stable isotope is deliberately added. Both of these processes usually give a high final *a*. However, it may be necessary to use a target of the same element or it may be necessary to add extra mass of the same element in order for the separation process to work. In this case, carrier is added deliberately and *a* will usually be low.

It should be noted that a carrier does not necessarily need to be of the same element. When labelling a radiopharmaceutical with a chelator and metal ions, any ion fitting into the chelator will compete. An example is labelling a peptide with ^{111}In, when the activity will usually be delivered as $InCl_3$ in a weak acid. By sampling the activity with a stainless steel needle, Fe ions will be released and will probably completely ruin the labelling process by outnumbering the ^{111}In atoms.

4.5.2. Separation methods, solvent extraction, ion exchange, thermal diffusion

After irradiation, the small amount of desired radioactivity (of the order of nanomoles) usually needs to be separated from the bulk of the target in a suitable form for the following labelling process and at high *a*. The separation time should be related to the half-life of the radionuclide and should take at most one half-life. Solid targets usually have to be dissolved, which is simple for salts such as NaI but more complicated for, for example, Ni foils where boiling aqua regia may have to be used. To speed up this process, the Ni foil can be replaced by a pressed target of Ni powder that will increase the metal surface and will speed up the dissolving process.

In general, two principles are used: liquid extraction and ion exchange. In liquid extraction, usually two liquids that do not mix are used, e.g. water and an organic solvent. The target element and the produced activity of another element should have different relative solubility in the liquids. The two liquids and the dissolved target are mixed by shaking, after which two phases are formed. The phase with a high concentration of the wanted radioactive product is sampled and is usually separated again one or more times to reduce the target mass in that fraction. The relative solubility can be optimized by varying the pH or by adding a complexing agent.

In the ion exchange mechanism, an ion in the liquid phase (usually an aqueous phase) is transferred to a solid phase (organic or ceramic material). To maintain the charge balance, a counter ion is released from the solid phase. This ion may be a hydrogen ion. In the ion exchange mechanism, the distribution ratio is often a function of the pH. Furthermore, complexing agents can be used to modify the distribution ratio. The dissolved target is adjusted to obtain the right

pH and other separation conditions, and is then put on to a column containing the ion exchange material. The optimal separation conditions would be that the small mass of desired radioactivity but not the bulk target material sticks to the column. The column can then be small, and after washing and change of pH, the desired activity can be eluted in a small volume. Under other conditions, large amounts of ion exchange material have to be used to prevent saturation of binding sites and leakage of the target material. This also means that large liquid volumes have to be used, implying poorer separation. The two techniques are often performed together by using liquid extraction to reduce the target mass, after which ion exchange is used to make the final separation.

Occasionally, thermal separation techniques may be applied, which have the advantage that they do not destroy the target (important when expensive enriched targets are used) and that they lend themselves to automation. As an example of such dry methods, the thermal separation of ^{76}Br ($T_{1/2}$ = 16 h) is described. The target is $Cu_2{}^{76}Se$, a selenium compound that can withstand some heat. The nuclear reaction used is ^{76}Se(p, n)^{76}Br.

The process is as follows:

(a) The target is placed in a tube and heated, under a stream of argon gas, to evaporate the ^{76}Br activity by dry distillation (Fig. 4.16);
(b) A temperature gradient is applied to separate the deposition areas of ^{76}Br and traces of co-evaporated selenide in the tube by thermal chromatography;
(c) The ^{76}Br activity deposited on the tube wall is dissolved in small amounts of buffer or water.

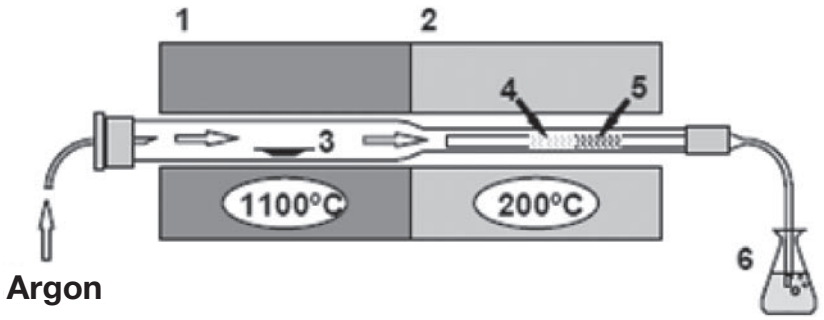


FIG. 4.16. A schematic description of the ^{76}Br separation equipment: (1) furnace, (2) auxiliary furnace, (3) irradiated target, (4) deposition area of selenium, (5) deposition area of ^{76}Br, (6) gas trap.

Separation yields of 60–70% are achieved by this method, with a separation time of about 1 h. Since dry distillation permits the extraction of radiobromine without destroying the target, the Cu_2Se targets are reusable. Considering the rather expensive ^{76}Se-enriched target material, this is a practical prerequisite for this type of production. The chemical form of the ^{76}Br activity after separation, analysed by ion exchange high performance liquid chromatography and thin-layer chromatography, was almost exclusively found to be bromide.

4.5.3. Radiation protection considerations and hot-box facilities

Besides the desired activity, the irradiated target usually contains a number of other radionuclides of varying elements, half-lives and γ energies. The presence of such contaminants needs to be taken into account when planning radiopharmaceutical labelling. An example is the production of ^{35}S using the reaction ^{35}Cl(n, p)^{35}S. At first glance, NaCl would be a suitable target due to the low atomic weight of sodium, a single isotope (^{23}Na) and a salt that is easy to dissolve. However, ^{23}Na has a huge thermal neutron cross-section for producing ^{24}Na, which has a half-life of 15 h and abundant γ energies up to 2.75 MeV. This target would be extremely hot, demanding lead protection more than 30 cm thick. If instead KCl were used, the emitted γ radiation energy would be substantially lower and decay times shorter.

After irradiation, the target is usually stored before processing to allow any short lived radionuclides to decay. Depending on the half-life, this ‘cooling period’ can be from minutes to months, but should not exceed one half-life of the desired radionuclide. The place used for this depends on the source activity and the energy and abundance of the γ emissions. Separation of fairly pure β and γ emitters may require just some distance and some plastic shielding, and can be performed in a standard fume hood, while targets with a high γ emission need significant lead shielding.

Handling reactor or accelerator produced radioactivity of the order of several hundred gigabecquerels requires adequate radiation protection, usually in the form of lead shields, hot-boxes, lead shielded fume hoods and laminar air flow benches. Typical lead thicknesses required by common radionuclides are indicated in Table 4.5.

The radioactive target and the radionuclide separation is often the first step in labelling a radiopharmaceutical. The hot-box then has to fulfil the requirements both to protect the operator from the radiation and to protect the pharmaceutical from the surroundings. The first step usually requires a negative pressure hood to prevent eventual airborne radioactivity to leak out into the laboratory, while the second step requires a high positive pressure to be applied across the pharmaceutical to avoid contact with less pure air from the laboratory.

TABLE 4.5. DOSE RATES AND LEAD SHIELDING REQUIRED FOR DIFFERENT RADIONUCLIDES, DETERMINED BY THE GAMMA RADIATION ABUNDANCE AND ENERGY[a]

	Dose rate (mSv/h) at 1 m per TBq			
	^{99m}Tc	^{111}In	^{18}F	^{124}I
	18	81	135	117
	Thickness of lead shield (cm) giving 1 μSv/h			
TBq	^{99m}Tc	^{111}In	^{18}F	^{124}I
0.1	0.28	1.0	5.8	20
1.0	0.36	1.3	7.1	22
10.0	0.43	1.6	8.5	27

[a] Calculations made with RadProCalculator (http://www.radprocalculator.com/).

These contradictory conditions are usually handled by having a box in the box, i.e. the pharmaceutical is processed in a closed facility at over pressure placed in the hot-box having low pressure. The classical hot-box design, with manipulators to manually process the radioactivity remotely, as seen in Fig. 4.17, is gradually being replaced by lead protected chambers housing an automatic chemistry system or a chemical robot making the pharmaceutical computer controlled.

FIG. 4.17. Examples of modern hot-box designs (courtesy of Von Gahlen Nederland B.V.).