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*Production of Medical Radionuclides*

by:

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# **Production of Medical Radionuclides**

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# PRODUCTION OF MEDICAL RADIONUCLIDES

## STATEMENT OF OBJECTIVES

The primary purpose of this lesson is to provide a fundamental understanding of the basic concepts and activities associated with the production of radionuclides for medical diagnosis, therapy, and research. The lesson presents the basic principles of nuclear reaction physics, methods of target irradiation for radionuclide production, and considerations associated with recovery of nuclides from irradiated targets. Some practical specific examples are presented to help understand the principles. The lesson concludes with a description of various approaches to production of  $^{99}\text{Mo}$ .

Upon successful completion of this material, the reader should be able to:

1. write basic nuclear reaction equations involved in the production of medical radionuclides.
2. calculate and predict whether a reaction process is energetically favored.
3. discuss factors that determine the yield of a particular radionuclide production mechanism.
4. describe the basic operation principles for linear and cyclotron particle accelerators.
5. describe the basic operation principles for a nuclear reactor.
6. discuss the various basic considerations associated with handling and processing irradiated targets to recover and purify radionuclides.
7. describe and evaluate various methods for production of  $^{99}\text{Mo}$ .

# COURSE OUTLINE

## I. INTRODUCTION

## II. GENERAL PRINCIPLES

### A. Nuclear reactions

1. Reaction energetics
2. Reaction yields, cross-sections and excitation functions
3. Thick target considerations
4. Accelerators
5. Reactors
6. Reaction mechanisms
7. Production of nuclides by neutrons

### B. Recovery and Purification of Radionuclides

1. Methods
2. Chemistry and choice of target material
3. Chemistry and specific activity
4. Facilities for Target Processing

## III. PRODUCTION OF Mo-99 FOR THE Mo-99/Tc-99m GENERATOR

### A. Reactor Production

### B. Accelerator Production

## IV. CONCLUSION

# PRODUCTION OF MEDICAL RADIONUCLIDES

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## INTRODUCTION

The practice of modern nuclear medicine depends upon the reliable regular supply of radionuclides in the proper chemical and physical form for preparation of generators, pharmaceuticals, and calibration sources. Production of the radionuclides used in the clinic and laboratory by practicing nuclear medicine professionals must be done in highly specialized facilities by personnel capable of performing several activities. These include irradiating proper target materials in particle accelerators or nuclear reactors, safely handling the highly radioactive targets, recovering and purifying the desired nuclides, properly disposing of or storing the radioactive wastes, and distributing the products. These activities must be performed by scientists, engineers and technicians specialized in various aspects of physics, chemistry, materials science, and remote handling.

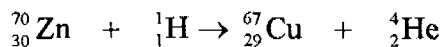
The purpose of this lesson is to give the reader an appreciation for the full scope of radionuclide production and its critical importance to the practice of nuclear medicine. The reader successfully completing this module will understand the basic considerations in choosing a target material for irradiation, the nuclear processes that occur during irradiation, and the fundamental operations that must be performed in order to recover, purify, and distribute the radionuclide. Examples will be provided describing the production of a few radionuclides of specific significance to diagnostic and therapeutic nuclear medicine.

## GENERAL PRINCIPLES

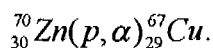
### Nuclear Reactions

The production of a radionuclide in a target material depends upon nuclear reactions being induced in the nuclei of atoms in the target. In a nuclear reaction, an atomic nucleus in the target interacts with another atomic nucleus, an elementary particle, or a photon to produce one or more other nuclei, and possibly other elementary particles. The new nucleus will have a different number of protons or neutrons than were present in the target, thus a new isotope or element is formed during a nuclear reaction. These reactions can be induced by placing the target material in a beam of accelerated charged particles or in a flux of neutrons. In this section of the lesson the nomenclature, energetics and mechanisms of nuclear reaction processes are presented.<sup>1</sup> These ideas are relevant in determining the type of irradiation that should be used and the nature of the target material that must be used to produce the desired nuclides.

Consider the example in which a target containing zinc is placed in a beam of accelerated protons (hydrogen ions). A naturally occurring sample of zinc (atomic number 30) contains five stable isotopes: Zn-64 (48.6%), Zn-66 (27.9%), Zn-67 (4.1%), Zn-68 (18.8%) and Zn-70 (0.6%).<sup>2</sup> Thus there are five different zinc nuclei with which the incident protons might react, and therefore a wide variety of potential nuclear reactions that might occur. For the sake of this discussion, consider the production of Cu-67, a nuclide currently being evaluated for its therapeutic application in the treatment of certain types of lymphoma. If an incident proton collided with a Zn-70 nucleus resulting in the capture of that proton by the nucleus followed by the subsequent ejection of an alpha particle (the nucleus of a helium atom), Cu-67 would result. This reaction is represented in standard nuclear reaction equation notation as follows:



A shorthand representation of this reaction equation is



In this notation the chemical symbol left of the parenthetical expression is the target nucleus and the chemical symbol to the right is the product nucleus. The left-most symbol within the parentheses is the incident particle and the right-most symbol is the ejected particle. The common formalism is to represent hydrogen ions with the symbol "p" and helium nuclei (alpha-particles) with symbol "α". Whether this reaction will occur or not depends on several factors governed by natural physical laws requiring conservation of energy, mass, and momentum during the reaction. Applying these laws allows one to predict whether the reaction can proceed as written and under what conditions.

### Reaction energetics

Every nuclear reaction is accompanied by an energy change due to transformation of mass during the process. The energy change during a nuclear reaction is called the Q value for the reaction and is defined by Einstein's equation as follows:

$$Q = (\text{sum of reactant masses} - \text{sum of product masses}) c^2$$

where c is the velocity of light. It is evident from this equation that if the sum of the reactant masses is greater than the sum of the product masses, a positive value of Q is obtained. This means that there is a net loss in mass during the reaction process that is conserved by the release of energy. The reaction is said to be exoergic. Conversely, if the sum of the reactant masses is less than the sum of the product masses, a negative value of Q is obtained; energy will be required to cause the reaction to proceed as it is written. From Einstein's equation it is relatively simple to show by dimensional analysis that 1 atomic mass unit is equal to 931.5 million electron volts (MeV) of energy as follows:

$$1 \text{ amu} = 1.662 \times 10^{-24} \text{ g}$$

$$1 \text{ kg} = 1 \times 10^3 \text{ g}$$

$$1 \text{ Joule} = 1 \frac{\text{kg} \cdot \text{m}^2}{\text{s}^2}$$

$$1 \text{ eV} = 1.6016 \times 10^{-19} \text{ Joule}$$

$$1 \text{ MeV} = 1 \times 10^6 \text{ eV}$$

$$E = mc^2 = (1 \text{ amu} \times \frac{1.66 \times 10^{-24} \text{ g}}{\text{amu}} \times \frac{1 \text{ kg}}{10^3 \text{ g}}) \times (2.9979 \times 10^8 \frac{\text{m}}{\text{s}})^2 = 1.492 \times 10^{-10} \text{ Joule}$$

$$E = (1.492 \times 10^{-10} \text{ Joule}) \times \frac{1 \text{ eV}}{1.6016 \times 10^{-19} \text{ Joule}} \times \frac{1 \text{ MeV}}{10^6 \text{ eV}} = 931.5 \text{ MeV}$$

If one knows the atomic masses of the particles involved in a proposed nuclear reaction process, it is easy to calculate the Q value for the reaction. There are tabulations available from which one can find the following atomic masses for the particles in the example:<sup>1</sup>

$$\text{Zn-70} = 69.9253 \text{ amu}$$

$$\text{Cu-67} = 66.9277 \text{ amu}$$

$$\text{H-1} = 1.0078 \text{ amu}$$

$$\text{He-4} = 4.0026 \text{ amu}$$

Applying these numbers to the calculation of Q for the example reaction, a value of +2.608 MeV is obtained. Thus, if the proton gets into the Zn-70 nucleus this reaction is favored energetically. However, some other factors must also be considered in order to evaluate the actual conditions necessary to induce the reaction.

Due to the very short range of nuclear forces, a nuclear reaction can only occur when the bombarding charged particle is actually incorporated into the nucleus of the target atom. Since, in this example, both the bombarding particle and the nucleus are positively charged, there is a very large barrier of repulsion that must be overcome. This is called the Coulomb barrier,  $V_c$ , and its magnitude can be approximated by classical charged particle mechanics. The energy of repulsion between a spherical nucleus of charge  $Z_2e$  (where  $Z_2$  is the atomic number and

e is the electrostatic charge) with radius  $R_2$ , and a bombarding particle of charge  $Z_1e$  with radius  $R_1$ , when the two are just in contact is given by:

$$V_c = \frac{Z_1 Z_2 e^2}{R_1 + R_2}$$

Expressing the radii in fermis (1 fermi =  $10^{-13}$  cm), this equation becomes<sup>1</sup>

$$V_c = 1.44 \frac{Z_1 Z_2}{R_1 + R_2} \text{ MeV}$$

Given that  $R = 1.5$  fermi for a proton and 6.2 fermi for a Zinc nucleus, the coulomb barrier for the example reaction would be 5.61 MeV.

For an exoergic reaction, as in this example, the kinetic energy of the incident particle must exceed the energy of the Coulomb barrier in order to penetrate into the nucleus. This energy required to initiate the nuclear reaction of interest is called the effective threshold energy. In this example, then, the effective threshold energy for the reaction is 5.61 MeV. This implies that if the kinetic energy of the accelerated proton exceeds this value, Cu-67 would be produced in the zinc target. This value is consistent with experimental observation.

If a reaction is found to be endoergic (negative Q value) the effective threshold energy is evaluated in a slightly different manner. One should evaluate both the Q value and the Coulomb barrier energy for the reaction. The threshold energy will be the greater of the two values. This analysis works well for reactions between light incident particles and significantly heavier target nuclei. If the incident particle and the target have similar masses then energy will also be required to conserve momentum during the reaction. When two objects collide, the total momentum is conserved before and after the collision. Thus, part of the kinetic energy of the bombarding particle is transferred to the recoil of the product nucleus. Since momentum is proportional to mass, the additional energy for momentum conservation is determined by the ratio of the total mass of the system [incident particle mass ( $m$ ) + product nucleus mass ( $M$ )] over the product nucleus mass. Thus the effective Q value,  $T_m$ , is determined as follows:

$$T_m = Q \frac{(m + M)}{M}$$

Several factors would determine the amount of Cu-67 that would be produced if a zinc target were bombarded with protons with energy in excess of 5.61 MeV. The most important of these are discussed in the following sections and include: (1) the number of Zn-70 atoms placed in the beam; (2) the number of protons per unit time striking the target; (3) the probability that a proton will actually collide effectively with a Zn-70 nucleus giving rise to the nuclear reaction; and (4) the duration of the bombardment.

### ***Reaction Yields, Cross-Sections, and Excitation Functions***

Since only 0.6% of the zinc atoms are Zn-70 in a target made of naturally occurring zinc, only 0.6% of all the zinc atoms effectively struck by a proton will lead to Cu-67 via the example reaction. Other nuclear reactions will possibly occur between protons and the various zinc isotopes giving rise to Cu-67 as well as other products that may be undesirable in the target. If an equivalent target were prepared with zinc that has been enriched in Zn-70, then the yield of Cu-67 from the model reaction would be enhanced in proportion to the enrichment, and the amount of contaminating products from reactions on other nuclides would be decreased. Enriched targets are significantly more expensive than natural targets. This must be considered when choosing a production mode for a particular nuclide. When enriched targets are used, a process to recover the target material for successive irradiations is one method that is used to mitigate the increased cost.

The chemical and physical form of the target will also determine the number of Zn-70 atoms presented to the beam. For example, a target made of a zinc metal foil would have more Zn-70 atoms per unit area exposed to the beam than a target of the same geometry composed of zinc oxide powder. For maximum yield one would attempt to prepare a target with the largest possible density of target atoms per unit volume. However, other factors also play a role in the choice of target material such as ease of fabrication, the ability of the material to withstand the

bombardment, and the ease with which the target can be processed after bombardment. These factors will be discussed in more detail later in the lesson.

The number of particles per unit time impinging on the target (beam current or particle flux) plays a key role in determining the production yield from a particular target. The number of effective collisions in the target increases in direct proportion to the number of incident particles. So, all else being equal, a beam current of 100 microamperes would produce twice as much nuclide as a beam current of 50 microamperes. The mathematical expression demonstrating this will be presented later. As beam current increases, however, issues associated with the ability of the target to withstand the irradiation become important.

If a Zn-70 target were bombarded with protons of energy in excess of 5.61 MeV, only a very small fraction of the zinc nuclei would actually be effectively struck by protons. This is because the space between the nuclei is large relative to the size of a nucleus so there is a significantly greater chance of an incoming proton to miss a zinc nucleus than there is to strike one for an effective collision. The probability of a particle striking a nucleus and inducing a particular nuclear reaction is called the cross section for the reaction, symbolized  $\sigma$ , with units of area. The cross section for a collision between a fast particle and a target nucleus is never greater than twice the geometrical cross-sectional area of the nucleus. The radius of the largest target nucleus is about  $10^{-12}$  cm, so the nuclear cross sectional area will have a magnitude of  $10^{-24}$  cm<sup>2</sup> (recognizing that the area of a circle is proportional to the square of its radius). A cross section of this magnitude is considered very large in terms of reaction probability. In fact, it is considered to be a target area "as big as a barn," so the common unit of cross section is called the "barn" and has a magnitude of  $1 \times 10^{-24}$  cm<sup>2</sup>. The accepted symbol for this unit is **b**. For example, a reaction with a cross section of 3 mb, has an actual cross section of  $3 \times 10^{-3} \times 10^{-24}$  cm<sup>2</sup>, or  $3 \times 10^{-27}$  cm<sup>2</sup>.

For a beam of particles striking a thin target (infinitesimal beam attenuation as it traverses the target), the cross section for a particular reaction process is defined mathematically as:

$$\sigma_i = \frac{R_i}{Inx}$$

In this equation  $R_i$  is the number of processes of interest occurring per unit time,  $I$  is the number of incident particles per unit time,  $n$  is the number of target nuclei per cubic centimeter, and  $x$  is the target thickness in centimeters. This equation may be used to calculate the value of a cross-section for a given reaction process under a fixed set of experimental conditions. Consider the following example.

A target is prepared by electroplating 7.85 mg of enriched Zn-70 metal as a 1.0 cm diameter circle on a target backing. The target is bombarded for 5.0 minutes with a 1.0-microampere beam of 15 MeV protons. At the end of bombardment, the Cu-67 radioactivity in the target is measured to be  $4.5 \times 10^5$  disintegrations per minute (dpm). From this data the cross-section for the example reaction can be calculated under the specified experimental conditions assuming that this is the only reaction leading to Cu-67. In order to do this, the values of  $R_i$ ,  $I$ ,  $n$ , and  $x$ , with the proper units, must be determined and substituted into the expression for  $\sigma_i$  as follows.

The value of  $R_i$  is calculated by determining the number of Cu-67 atoms produced per unit time during the target irradiation. This may be calculated by applying the equation relating disintegration rate and number of decaying atoms:

$$\frac{dN}{dt} = \lambda N$$

In this equation  $N$  is the number of atoms decaying at the rate  $dN/dt$  and  $\lambda$  is the decay constant for the nuclide whose radioactivity is being measured. In this example,  $dN/dt$  is equal to  $4.5 \times 10^5$  dpm and with the half-life of Cu-67 of 61.92 hours,

$$\lambda = \frac{0.693}{t_{1/2}} = \frac{0.693}{61.92 \text{ hr}} = 0.01119 \text{ hr}^{-1}$$

Thus,



$$4.5 \times 10^5 \text{ min}^{-1} \times 60 \frac{\text{min}}{\text{hr}} = (0.01119 \text{ hr}^{-1})N$$

or

$$N = 2.4 \times 10^9 \text{ atoms Cu-67.}$$

Since these atoms of Cu-67 were produced in a 5.0 minute irradiation

$$R_i = \frac{2.4 \times 10^9 \text{ atoms}}{5.0 \text{ min}} = 4.8 \times 10^8 \frac{\text{atoms}}{\text{min}}$$

In order to calculate the value of  $I$  (the number of protons striking the target per unit time), some basic definitions must be recalled. An ampere is defined as 1 coulomb/s of charge and 96,500 coulomb is equal to 1 mole of charge. Knowing this,  $I$  can be calculated as follows:

$$I = 1.0 \times 10^{-6} \frac{\text{coul}}{\text{s}} \times \frac{1 \text{ mole H}^+}{96,500 \text{ coul}} \times \frac{6.02 \times 10^{23} \text{ H}^+}{\text{mole H}^+}$$

or

$$I = 6.2 \times 10^{12} \frac{\text{H}^+}{\text{s}}$$

There is sufficient information to calculate  $n$  and  $x$  independently. However, by dimensional analysis the product of the two can also be calculated without going through an independent calculation of each. Recalling that  $n$  is the number of target atoms per cubic centimeter and  $x$  is the thickness of the target in cm, the units of the product of these two parameters can be determined:

$$nx = \left( \frac{\text{atoms}}{\text{cm}^3} \right) \text{cm} = \frac{\text{atoms}}{\text{cm}^2}$$

It is common practice for experimenters in targetry for radionuclide production to express the target "thickness" in terms of mass per unit area, thus making it a straight forward calculation to get atoms per unit area to substitute for the product of  $n$  and  $x$  in the cross-section expression. In this analysis, the mass of Zn per unit area in the target is first calculated, followed by the number of Zn atoms per unit area. The 7.85 mg target covers a circle having a diameter of 1.0 cm, or a radius of 0.5 cm. Therefore the mass per unit area of target is

$$\frac{\text{mass Zn}}{\text{cm}^2} = \frac{7.85 \text{ mg}}{\pi (0.5 \text{ cm})^2} = 10 \frac{\text{mg}}{\text{cm}^2}$$

Recalling that the atomic weight of Zn-70 is 69.93 the number of Zn-70 atoms per  $\text{cm}^2$  can be calculated.

$$\frac{10 \text{ mg}}{\text{cm}^2} \times \frac{1 \text{ mmol}}{69.93 \text{ mg}} \times \frac{6.02 \times 10^{20} \text{ atoms}}{\text{mmol}} = 8.60 \times 10^{19} \frac{\text{Zn-70 atoms}}{\text{cm}^2}$$

Now the cross-section for the reaction  $^{70}\text{Zn}(p,\alpha)^{67}\text{Cu}$  using 15 MeV protons can be calculated to be

$$\sigma_i = \frac{4.8 \times 10^8 \text{ min}^{-1}}{6.2 \times 10^{12} \text{ s}^{-1} \times \frac{60 \text{ s}}{\text{min}} \times 8.60 \times 10^{19} \text{ cm}^{-2}} = 1.5 \times 10^{-26} \text{ cm}^2 \times \frac{1 \text{ barn}}{10^{-24} \text{ cm}^2} \times \frac{1 \text{ mbarn}}{10^{-3} \text{ barn}} = 15 \text{ mbarn}$$

Cross section measurements for reactions occurring with low energy beams (e.g. < 100 MeV for protons) show a relatively strong dependence on the energy of the bombarding particle. This dependence of cross section on

energy for a particular reaction to yield a specific product is called the excitation function,  $\sigma_i(E)$ . The common method of presenting excitation function data in the literature is as plots of cross section versus incident particle energy. Figure 1 shows the experimental and theoretical excitation function for the example reaction.<sup>3</sup> Excitation function data guide the scientist in the selection of optimum irradiation conditions to maximize yield of desired radionuclides while minimizing the production of undesirable nuclides in a “thick” target.

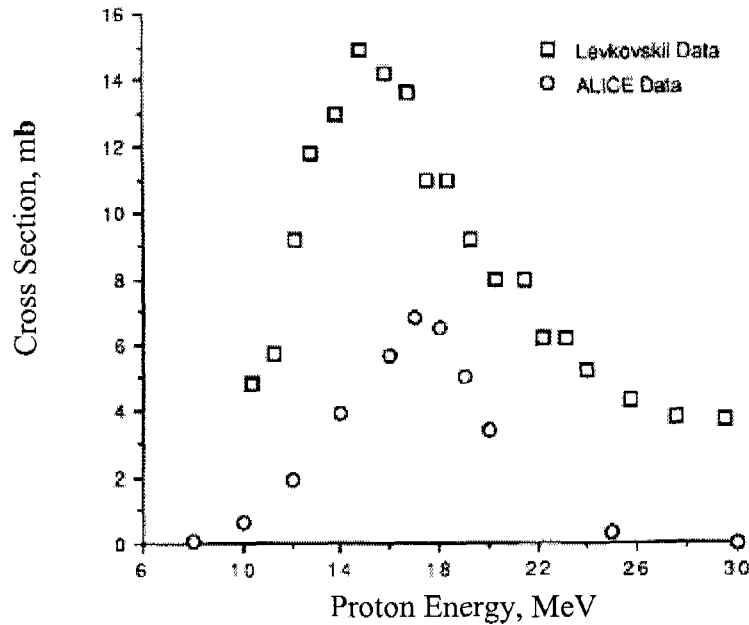


Figure 1. Experimental and ALICE calculated excitation functions for the  $^{70}\text{Zn}(p,\alpha)^{67}\text{Cu}$  Reaction.<sup>3</sup>

### Thick Target Considerations

Nuclide production targets are generally “thick” relative to the thin foils used in measurement of cross sections. When a beam of charged particles traverses a target material most of these particles undergo interactions with target nuclei that do not lead to nuclear reactions, but impact the beam in two important ways.<sup>4</sup> The incident particles will lose energy as they pass through the target, and the particles will be deflected from their incident path leading to physical broadening of the beam.

Since the accelerated particles are necessarily charged, they are surrounded by a coulombic electric field. Therefore, even if an individual particle does not collide with a target nucleus, it will still interact with the electron clouds surrounding the target nuclei transferring a small fraction of its kinetic energy and deflecting it to at least a very small degree from its initial direction. If the incident particle passes a target atom at a distance that is considerably greater than the atomic radius, the interaction will be relatively mild, distorting the surrounding electron cloud of the target atom. There are some particles of the beam that will collide directly with an electron in a target atom ejecting it with considerable kinetic energy. In such a collision the beam particle will experience very little change in its direction of motion, though a substantial amount of energy will be lost by the particles. The primary effect of these processes is a loss of kinetic energy by the particles in the beam with a slight broadening in the beam profile.

Some beam particles will collide elastically with target nuclei without inducing a nuclear reaction process. In this interaction the particle will lose very little kinetic energy since in most nuclide production experiments the masses of the target nuclei are large compared to the incident particle. However, these particles will be deflected significantly from the initial incident direction. Thus the primary effect of this type of collision is a reduction of beam intensity in the forward beam direction.

If the target is sufficiently thick, these phenomena will cause the beam to be completely stopped in the target with its full energy being deposited in the target. The stopping power,  $S$ , defined as the average change in beam

energy per unit thickness of target ( $S = dE/dx$ ) is a very important parameter in determining optimum target thickness for best product yield and for calculating the amount of heat that will be deposited in the target.<sup>5</sup> The form of this function is very much dependent upon both the beam energy and the nature of the target. As an example, incident proton energies of less than about 100 MeV will have values of  $S$  dominated by a  $1/v^2$  dependence in most target materials, where  $v$  is the initial particle velocity. Thus the relative magnitude of the energy loss per unit target thickness increases significantly as the incident particle energy decreases.

Another important observation concerning the change in the beam as it traverses a target is that a spread in the particle energy will develop so that a narrowly mono-energetic incident beam will acquire an energy spread. The extent of this spread will depend upon the nature of the incident particles, the nature of the target material, and the physical thickness of the target. The full-width-at-half-maximum (FWHM) of the energy distribution is a measure of this "energy straggling" and it increases with the depth of the beam in the target.<sup>6</sup>

A quantitative treatment of the effects discussed above is beyond the scope of this lesson. However, there are several important qualitative implications that should be mentioned. Ultimately, the yield of a particular nuclide in an irradiated target will be influenced by the magnitude of the beam current and the chemical composition and physical configuration of the target. Consider again the example of production of Cu-67 by bombardment of Zn-70 with protons. Inspection of the excitation function (Figure 1) reveals that there is a measurable cross-section for production of Cu-67 over the proton energy range of about 6 to 30 MeV, with a peak at about 15 MeV. A strategy for a production target might be to design it of appropriate mass and dimension to intercept the full diameter of an incident beam of about 30 MeV and of sufficient thickness to degrade the energy of the beam inside the target down to about 6 MeV. In this way, the full production peak for the (p, $\alpha$ ) reaction would be captured within the target, thereby giving the maximum possible yield. A zinc foil having a thickness of about 0.08 cm would be sufficient to degrade a 30 MeV beam to below 6 MeV, so in principal this would be the optimum thickness for production of Cu-67.

The problem with the above analysis is that it neglects the fact that other nuclear reactions which impact the quality of the final Cu-67 product must be considered. The calculated excitation function for the  $^{70}\text{Zn}(p,\alpha n)^{66}\text{Cu}$  reaction reveals a production threshold of about 18 MeV with a Cu-66 production peak of about 25 - 28 MeV.<sup>3</sup> Therefore, significant quantities of Cu-66 would be produced in the Zn-70 target if the incident beam energy were 30 MeV. The presence of this nuclide might not be a significant problem since its half-life is only 5.1 minutes, so delaying the process of separating the copper from the target would allow the Cu-66 to decay out. For example, if the process were delayed 60 minutes after bombardment, 99.9% of the Cu-66 would decay away while only 1.1 % of the Cu-67 would be lost to decay.

However, another competing reaction,  $^{70}\text{Zn}(p,\alpha 2n)^{65}\text{Cu}$ , does present a potentially significant problem with the target scenario described above. Copper-65 is a stable isotope of copper. Its presence in the final product would reduce the specific activity of the Cu-67. A significant application of Cu-67 is labeling of monoclonal antibodies for treatment of lymphoma.<sup>7</sup> The stable copper isotope competes with the Cu-67 for labeling sites during the pharmaceutical synthesis, thereby reducing the specific activity of the therapeutic compound. The calculated excitation function for the (p, $\alpha 2n$ ) reaction reveals a substantial cross-section at 30 MeV.<sup>3</sup> If the incident proton beam on the Zn-70 target is 30 MeV, then the final Cu-67 product would have a significant amount of Cu-65 contamination that cannot be removed chemically or by radioactive decay. The threshold energy for this Cu-65 production reaction is between 20 and 25 MeV.<sup>3</sup> So if a lower incident proton energy of 20 MeV were used, the Cu-67 production peak would be captured with little or no Cu-65 and Cu-66 production.

If the incident proton energy is reduced to 20 MeV, the target does not have to contain as large a mass of Zn-70 in order to capture the remainder of the Cu-67 production peak. A zinc target with a thickness of about 0.05 cm would be sufficient to completely stop an incident proton beam of 20 MeV. Furthermore, the target could be reduced to a thickness of about 0.025 cm so that the incident proton energy of 20 MeV would be degraded to 10 MeV before emerging from the back of the target. Since very little Cu-67 is produced at energies below about 10 MeV, this target configuration would produce virtually the same amount of Cu-67 as the 0.08-cm target. In this example there is considerable economic significance to keeping the target thickness to only that necessary to maximize the yield of the Cu-67. Zinc enriched to 98% Zn-70 presently costs about \$384 per milligram. A target with 1-cm diameter, which is 0.08-cm thick, would require about 450 mg of zinc, and thus cost about \$173,000, whereas the 0.025-cm target would require only about 140 mg of zinc and cost about \$54,000.

Another reason to minimize the thickness of the target is to reduce the amount of heat energy deposited in the target. All the beam energy deposited in a thick target becomes heat that must be effectively removed to maintain the target integrity.<sup>6</sup> If a zinc target received a 50 microampere current of 20 MeV protons and degraded the beam energy to 10 MeV, 500 watts of power would be deposited in the target. Depending upon the length of time the

target is irradiated, tens to hundreds of thousands of joules of heat energy would need to be carried away by a cooling agent to keep the target from being destroyed. Very often, high velocity water circulation around the target is used to accomplish the cooling. Experts in the field of thermal-hydraulics are called upon to help carefully engineer cooling systems so targets can be reliably cooled during irradiation.

One can see from the foregoing discussion that many factors must be considered in relation to irradiation of targets to yield useful quantities of radionuclides in a target. Beam energy, beam current, desired reaction cross-sections, reaction cross-sections for undesired nuclides, target configuration, target mass, and, stopping power ( $dE/dx$ ) are all critical parameters. Ultimately, the yield that can be expected from a given target configuration and irradiation is an empirically determined quantity. Production yields are generally expressed in units of activity of desired nuclide produced per unit mass of target per microamp-hour of irradiation time.

Most of the foregoing discussion has focused on a specific example in which accelerated protons are used to induce nuclear reactions. Any accelerated charged particles or neutrons generated in a reactor or accelerator can be used to induce nuclear reactions for nuclide production. Protons (p), deuterons (d), and alpha particles ( $\alpha$ ) are the most commonly accelerated particles used to induce the reactions to produce radionuclides. However, heavier nuclei, and even neutrons resulting from proton interactions with target materials in the accelerator, might also be used.

### *Accelerators<sup>1,8</sup>*

The two most commonly used accelerator types for isotope production are proton linear accelerators (linacs) and cyclotrons for accelerating protons and other light ions. All particle accelerators operate on the basic principle that a charged species, when placed in an electrical potential field, will acquire kinetic energy by electrostatic acceleration. Linacs accelerate the particles linearly down a length of evacuated pipe through a series of accelerating tubes, whereas cyclotrons accelerate them in a circular spiral inside a magnetic field. Both types require an ion source. This is a device that ionizes a gaseous species, usually in an arc or electron beam, then electrostatically draws the ions through a slit and focusing optics into the accelerator.

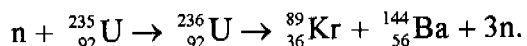
In a linac, the ions are accelerated in bunches through a series of segments made up of "drift tubes," with the accelerating potential on gaps between the tubes. The beam line is maintained at high vacuum. The potential at the first gap draws the ions into the first segment and accelerates them into the first drift tube toward the next gap. The electrical polarity at the gap is oscillating at radio frequency (rf), so that as the ion bunch approaches the gap it is attracted into the gap, then repelled through the gap into the next drift tube. In order to enter the accelerating gap at the right polarity the ions must be in each drift tube segment for one half of the oscillating cycle. The drift tubes shield the ions from the potential during the "wrong" phase of the rf cycle. As they gain velocity moving down the accelerator, the segments between the accelerator gaps must increase in length to remain in phase with the oscillating potential. Both negative and positive ions can be accelerated in a linac. Some facilities have the capability of accelerating both simultaneously by injecting them at the proper phase and frequency from separate ion sources. The ultimate energy attained by the ions is determined by the overall length of the accelerator. The beam intensity (ions per unit time) is determined primarily by the ion source.

Cyclotrons also accelerate ions across potential gaps that are oscillating at radio frequency. However, the ions are injected into a magnetic field instead of a drift tube. An electromagnet generates the magnetic field perpendicular to the plane of motion of the ions. The ions are generated near the center of a gap between two hollow semicircular vacuum chambers called "dees." The potential that accelerates the ions is applied across this gap. The frequency of oscillation of the potential is such that as the ions enter the gap twice in each full circle, the polarity is correct to accelerate the ions across the gap. The ions are then constrained to a circular motion. In the fixed magnetic field the radius of the circle of motion of the accelerated ions is determined by their velocity. Since the velocity increases with each rotation in the cyclotron, the radius of curvature increases, so that the ion beam spirals out from the center. The ultimate energy of the beam is determined by the number of cycles the ions make inside the accelerator. The beam can be "extracted" from the cyclotron at any point by neutralizing the charge on the ions, at which point they will revert to a linear motion tangent to the point of extraction. As with the linac, either positive or negative ions can be accelerated. Beam intensity is determined primarily by the output of the ion source.

### *Reactors<sup>1,8</sup>*

Presently, nuclear reactors with available irradiation positions in the operating core are necessary for neutron production of radionuclides. If the proper amount of fissionable material is contained in the proper geometry, a nuclear reaction can be initiated that will be sustained by the neutrons generated by the fissioning atoms. Most reactors use  $^{235}\text{U}$  as the fuel, depending upon the  $^{235}\text{U}(n,f)$  reaction for operation. When a uranium nucleus fissions

after neutron capture to yield two lighter nuclides, the reaction will also release one or more neutrons; an example is the reaction



Large amounts of energy are released when fission reactions occur, which is manifested as heat in the material. Thus if the fission process can be properly controlled, this heat energy can be used to generate steam to drive electrical power generating turbines. The amount and configuration of the fissionable material determines the amount of energy that can be produced by the reactor. In order for a sustained reaction to occur, at least one neutron created in a fission reaction must cause fission of another uranium nucleus. A quantitative measure of whether this condition exists is the “multiplication factor,”  $k$ . This is defined as the ratio of the number of fissions produced by a particular generation of neutrons to the number of fissions giving rise to that generation of neutrons.<sup>1</sup> This ratio must at least equal 1 in a given configuration of  ${}^{235}\text{U}$  in order to have a sustained reaction. If a sample of  ${}^{235}\text{U}$  is configured so that  $k$  is just equal to 1, the sample is said to be a critical assembly. If  $k$  is greater than 1, the assembly is supercritical. A practical reactor will have a  ${}^{235}\text{U}$  core assembly that is designed to have a multiplication factor that is greater than 1, and thus has excess reactivity. The reaction rate is controlled by putting materials into the core, usually in the form of rods that can absorb some of the neutrons and maintain the multiplication factor near 1. These control rods are important to keep the reactor “operating” at the desired power level and neutron flux (number of neutrons per square centimeter per second). Reactor fuel will generally be distributed in a moderator such as graphite or heavy water so that the neutrons will be “slowed” to near thermal energies to maximize the fission capture yield. At normal room temperatures the average energy of thermal neutrons is about 0.025 eV. However, some reactors are designed to have a relatively high flux of higher energy neutrons.

Many reactors are built for the primary purpose of producing neutrons for scientific research and for production of radionuclides. Such reactors will have access to neutron fluxes via insertion tubes or pneumatic systems so samples can be placed in the desired region for irradiation. If the samples have a relatively high cross section for neutron capture, the reactor operator must account for its presence in order to maintain proper reactor operation. Since the target material for production of molybdenum-99 is  ${}^{235}\text{U}$ , the operator must be aware of added reactivity in the reactor and operate accordingly. Great care must be taken in the design and operation of radionuclide production facilities inside a reactor core so that target integrity is maintained, yields optimized, and operations done safely. All reactors, whether for power, research, or radionuclide production are closely regulated to assure the safety of the worker, the public, and the environment.

If neutrons are used to produce nuclides, most often these are produced in a nuclear reactor. Since the uncharged neutrons have no Coulomb barrier to overcome in order to be assimilated by a target nucleus, there is a relatively high cross-section for “capture” of a neutron with thermal energies by a target nucleus. However, there is an energy barrier to emission of charged protons from the activated nucleus, so these neutron capture reactions often lead to “neutron rich” radionuclides that have applicability in nuclear medicine. To better understand this, it is instructive to consider in a qualitative way some of the proposed mechanisms of nuclear reaction processes that lead to new nuclides. Mathematical formulations of these mechanisms are used to model excitation functions for nuclear reactions for both neutrons and accelerated charged particles.

### *Reaction Mechanisms<sup>1</sup>*

The so-called “compound nucleus” mechanism can often explain the products obtained after a nucleus absorbs a new nuclear particle. The new nucleus, called the compound nucleus, attains statistical energy equilibrium whereby the incident kinetic energy of the particle is shared and re-shared among the nucleons (i.e., other neutrons and protons) in the target nucleus, with no particle emission. Some time after absorbing the particle ( $10^{-16} - 10^{-18}$  seconds), nucleons with sufficient energy to escape, and photons, are emitted giving rise to new nuclides. Since particles emitted will have relatively low kinetic energy in this model, they are viewed as “evaporating” from the nucleus in analogy to molecules evaporating from a hot drop of liquid. This model works best for accelerated particles of relatively low energy and for thermal neutrons. The model explains why the most probable reaction involving thermal neutrons is the  $n,\gamma$  reaction, in which a neutron is captured and the only emission is a gamma photon. The compound nucleus formed when a slow moving neutron is captured possesses an energy that is only slightly elevated and the probability of a single nucleon within the excited nucleus acquiring sufficient energy to escape is very low. Thus, the most probable mechanism for the release of the excess energy is by photon emission.

As the incident particle energy increases, a different mechanism more accurately predicts the products. It is called the “direct interaction” mechanism. In this model, the incident particle has a single interaction with one or a few nucleons in the target nucleus. This interaction occurs over a very short time range ( $\sim 10^{-22}$ s) without passing through the compound nucleus stage. As a result of this interaction the nucleons may be directly ejected from the target nucleus with kinetic energies considerably higher than those expected for “evaporated” particles. If the incident particle energy is sufficiently high, the initial direct interaction can lead to an “intranuclear” cascade where the struck nucleon in the original target nucleus interacts with one or more other nucleons ultimately ejecting one or more others.

Spallation reactions occur when the incident particle energy is in excess of about 100 MeV and leads to a suite of products ranging in mass from the target nuclei mass down. The product distribution peaks at about 10-20 mass units on the low-mass side of the target nuclei and drops off rapidly at lower masses. These products are explained by initial direct interaction processes, leading to intranuclear cascades, followed by evaporation processes from several different compound nuclei in the target. Due to the high energy of the incident particles, the probability of interaction with target nuclei is relatively low, so spallation yields are generally much lower than for reactions occurring at lower energies.

Most large atomic nuclei are unstable, and split into two nuclear fragments with the release of energy and neutrons. These so-called fission reactions can occur when either neutrons or charged particles are captured by nuclei of heavy atoms (atomic number generally greater than 80). Many well-known nuclides, both natural and man-made, have very high cross sections to fission upon capture of thermal neutrons, including, among others,  $^{233}\text{U}$ ,  $^{235}\text{U}$ ,  $^{239}\text{Pu}$ , and  $^{242}\text{Am}$ . Fission reactions induced by thermal neutron capture in a material lead to a variety of potential products. Figure 2 shows the excitation function for thermal neutron irradiation of a target containing  $^{235}\text{U}$  to cause fission reactions.<sup>1</sup> Figure 3 shows the relative yields of fission products of various masses formed after Uranium fission.<sup>8</sup> It is evident from this curve that a large number of nuclides will be produced in a  $^{235}\text{U}$  target exposed to a flux of thermal neutrons. One of the more important medical radionuclides is Mo-99, the parent nuclide to Tc-99m, and feed stock for the important Mo-99/Tc-99m generator. About 6% of all fission reactions induced by thermal neutrons in a U-235 target exposed to a thermal neutron flux will lead to a Mo-99 nucleus. Many other heavy nuclides not fissionable by thermal neutrons will undergo fission when bombarded by higher energy neutrons or charged particles.

The distribution of fission products due to these high-energy particle interactions is a strong function of the energy of the incident protons. Figure 4 is a comparison of the approximate mass distributions of the products from a Bi-209 target bombarded by 40, 400, and 4000 MeV protons.<sup>1</sup> At 40 MeV the predominant reactions are simple compound nucleus processes leading to a narrow suite of products with peak mass distribution just below the Bi-209 target mass. At 400 MeV there is a broader mass distribution peak between 160 and 210 amu due to spallation processes, and a secondary peak between 60 and 120 MeV due primarily to Bi-209 fission processes. At 4000 MeV there is a continuous distribution with no clear distinction between products from spallation and fission processes.

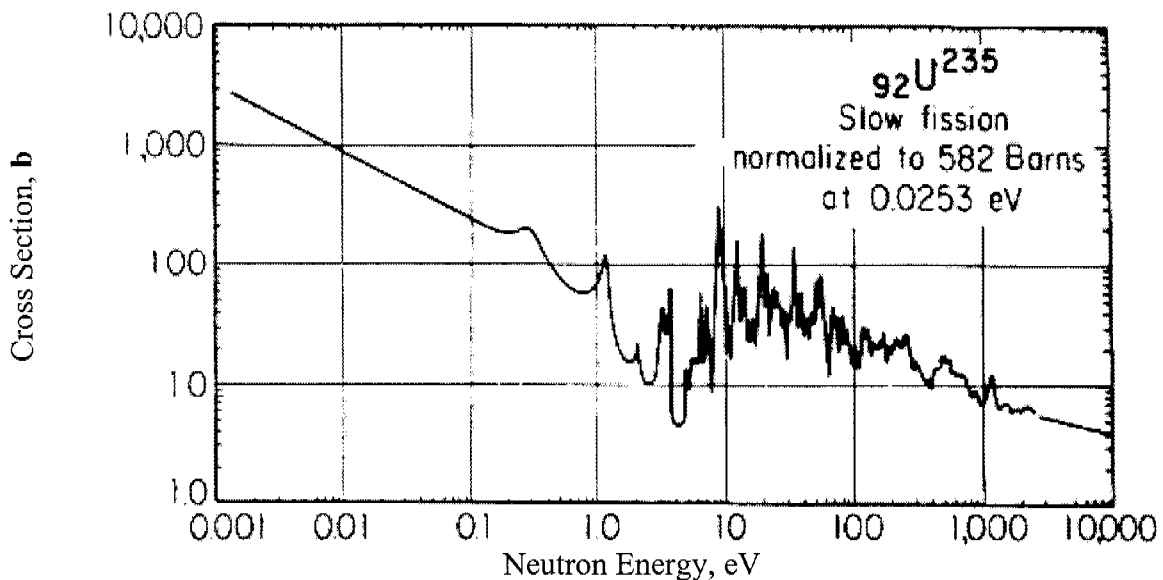


Figure 2. Excitation function for neutron fission on  $^{235}\text{U}$ .<sup>1</sup>

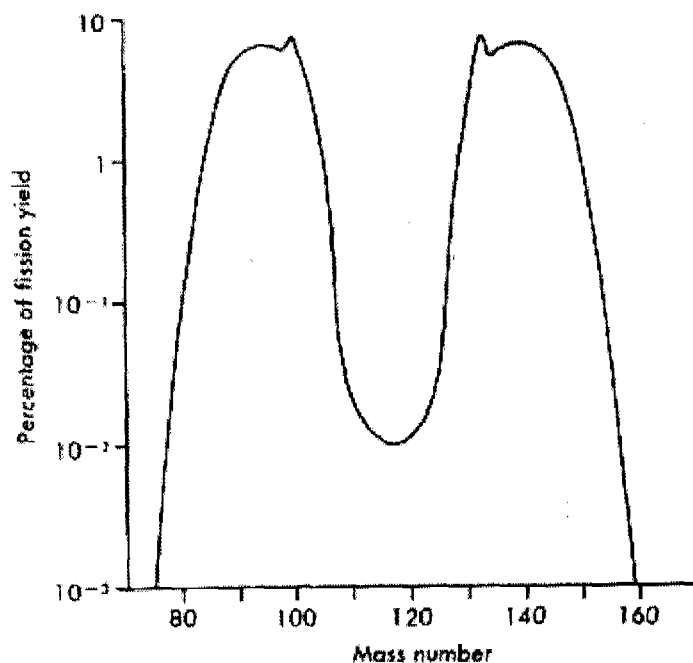


Figure 3. Fission product yield curve for uranium.<sup>8</sup>

### Production of Nuclides by Neutrons

Most of the preceding discussion has focused upon production of nuclides by accelerated particles. Now the discussion will turn to a more detailed consideration of production of nuclides by neutron bombardments in nuclear reactors. Nuclear reaction processes that can occur in three different neutron energy realms will be considered.<sup>9</sup> Neutrons released during normal fission processes in a nuclear reactor core will have kinetic energies of several thousand electron volts (eV). These neutrons are referred to as fast neutrons. As discussed earlier, neutrons with kinetic energies comparable to gas molecules at ordinary temperatures, called thermal neutrons, are much more efficient inducers of nuclear reactions than fast neutrons. Neutrons having a kinetic energy higher than thermal neutrons up to about 1000 eV are designated epithermal neutrons. Some nuclear reactors have a region in the core where relatively high fluxes of epithermal neutrons can be accessed.

Many important medical radionuclides can be produced via the  $(n,\gamma)$  reaction. For any given  $(n,\gamma)$  reaction the cross-section is highest for lower energy thermal neutrons and declines as the inverse of neutron velocity  $(1/v)$ .<sup>1</sup> As the neutron energy increases into the epithermal region,  $(n,\gamma)$  cross-sections show very large peak fluctuations over very narrow energy ranges. These fluctuations are called resonances. Figure 5 shows the excitation function for the  $(n,\gamma)$  reaction on a natural silver target that clearly shows the  $(1/v)$  dependence in the thermal neutron energy region and the resonance peaks in the epithermal realm.<sup>1</sup>

There are several factors that should be considered when planning to use an  $(n,\gamma)$  reaction to produce a medical radionuclide. Most nuclides produced by this route are used in therapeutic applications, taking advantage of the fact that many of the neutron rich nuclides decay by beta particle emission. Many of these are used to label a delivery molecule targeted for a specific therapeutic application. Most of these radiopharmaceuticals are effective only at relatively high specific activity. In this discussion, the specific activity is defined as the ratio of activity of desired nuclide to mass of all stable isotopes of the same element. This quantity is often expressed in units of mCi/mg. Since the product nuclide and the target isotope are of the same element, this ratio can be quite low when using the  $(n,\gamma)$  reaction. Obviously, targetry approaches that maximize desired nuclide yield while minimizing the mass of target material will give a product of highest specific activity. The following equation can be used to understand approaches to accomplishing this goal:

$$R_i = \phi N \sigma_i$$

$R_i$  is the number of reaction processes of the type desired,  $\phi$  is the flux of neutron particles per square centimeter per second,  $N$  is the number of target atoms, and  $\sigma_i$  is the cross section of the reaction. If the reaction is performed in as high a neutron flux as possible, then the target mass can be kept to a minimum while maintaining the production rate. Reactors commonly in use for production of radionuclides in the United States have thermal neutron fluxes ranging from about  $1.0 \times 10^{13} \text{ n s}^{-1} \text{ cm}^{-2}$  to about  $2.2 \times 10^{15} \text{ n s}^{-1} \text{ cm}^{-2}$ .<sup>9</sup> The highest flux in this range can produce over 200 times more activity in the same target mass as the lowest flux, and thus provide a product of 200 times higher specific activity.

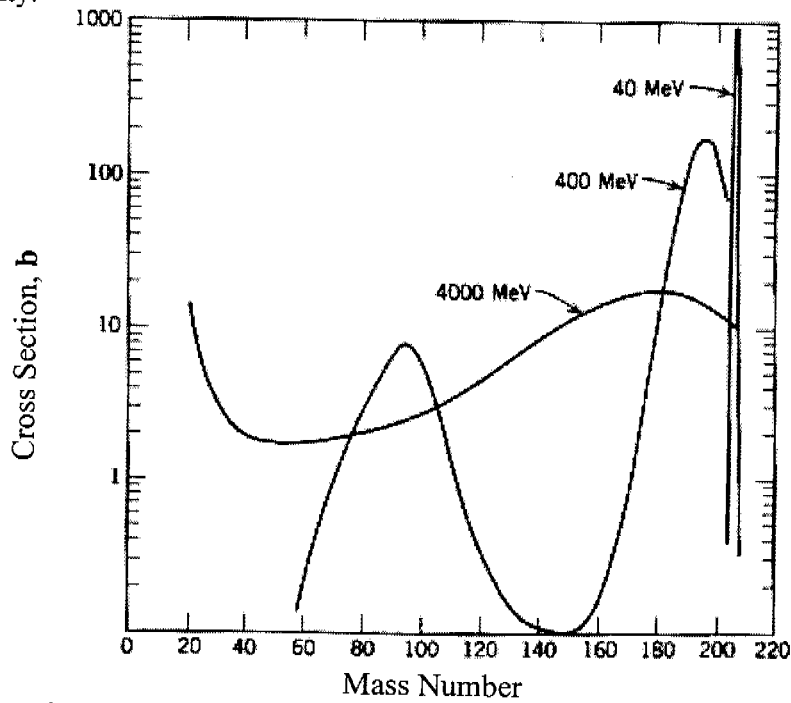


Figure 4. Approximate mass distributions of the products from a Bi-209 target bombarded with accelerated protons.<sup>1</sup>

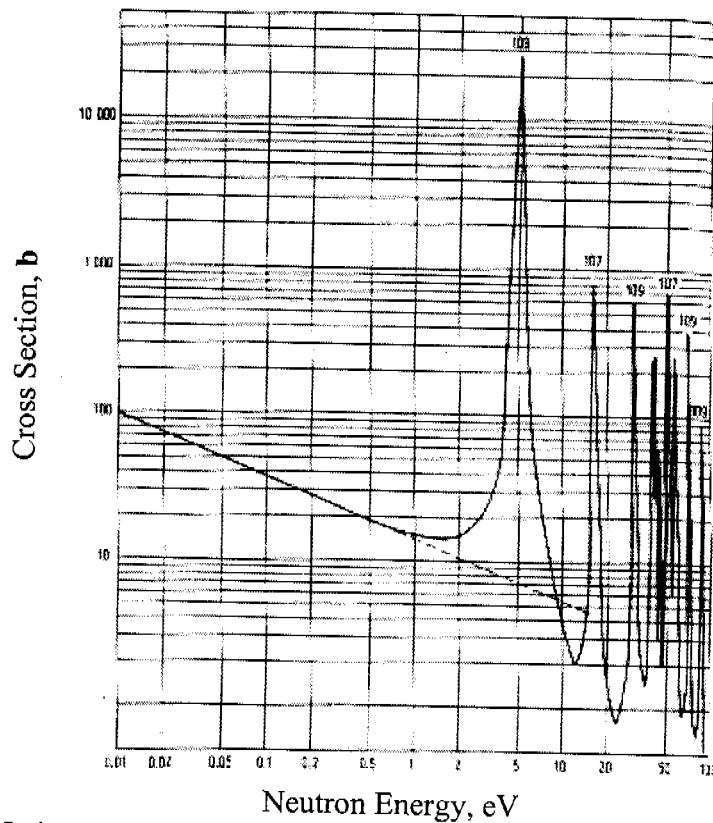


Figure 5. Excitation function for neutron capture on a natural silver target.<sup>1</sup>



Another important means to maximize the number of target nuclei placed into the reactor flux is to use targets enriched in the specific target nucleus. Consider the example of production of Sm-153 via Sm-152(n, $\gamma$ ) reaction. If a target containing naturally occurring samarium were used for the production, only 26.7% of the samarium atoms in the target would be Sm-152.<sup>2</sup> If instead a target were fabricated from samarium enriched to 98.3% in Sm-152, then for the same mass of target, there would be 3.7 times as much Sm-153 produced, and 3.7 times the specific activity. Furthermore, there would be a much lower amount of contaminant produced by neutron capture reaction on other stable samarium isotopes.

One approach to maximizing nuclide yield is to keep the target in the reactor flux as long as possible. There are two important factors to consider in determining length of the irradiation. For product nuclides of relatively short half-life, there will be a point in time during the irradiation when the rate of decay of the nuclide is equal to the rate of production. Some researchers refer to this as the "half-saturation" time, and equate this length of irradiation time to the half-life of the nuclide. Often in the literature, yields of nuclides from reactor production are reported as the half-saturation yields. The other factor that must be considered is the cross-section for neutron capture by the product nuclide. If this cross-section is large, then there will become a point in time when the rate of production of the nuclide is offset by the rate of neutron capture by the desired nuclide. In the literature, the cross-section of the reaction that consumes the desired nuclide is referred to as the "burn-up" cross-section. The burn-up cross-section can be quite large and must be considered when estimating the amount of irradiation time necessary to maximize nuclide yield.

One of the ways to reduce the "burn-up" loss of desired radionuclide is to use resonance reactions in the epithermal region of the neutron spectrum to induce the (n, $\gamma$ ) reaction. Figure 5 shows the excitation function for (n, $\gamma$ ) reactions on a silver target. This figure shows that the cross-section for the Ag-109(n, $\gamma$ )Ag-110 reaction is on the order of 20 to 100 barns in the thermal neutron energy realm of 0.01- 0.025 eV.<sup>1</sup> However, if the target were moved to an epithermal flux of 5 to 100 eV neutrons, resonance peaks are observed with cross-sections ranging from 100 to almost 30,000 barns. In this region, there would be a high production yield and there is a reduced cross-section for burn-up of the Ag-110.

One can sometimes take advantage of the high "burn-up" cross-section to produce a desirable nuclide in relatively high yield. Some significant medical nuclides are produced by the so-called double neutron capture reactions, (2n, $\gamma$ ). Possibly the best example is for the production of W-188. This nuclide is used as the parent of the W-188/Re-188 biomedical generator system.<sup>10,11</sup> Rhenium-188 decays by beta-emission with a 16.9 hour half-life, and also emits a 155 keV gamma photon that can be imaged. Because of its chemical similarity to technetium, this nuclide is being investigated as an excellent candidate for an array of therapeutic radiopharmaceuticals. The parent nuclide can be produced via the <sup>186</sup>W(2n, $\gamma$ )<sup>188</sup>W reaction. Keep in mind that this notation implies first a neutron capture by the W-186 nucleus to produce W-187, followed by neutron capture by the W-187 nucleus to yield W-188. The thermal cross section for the first reaction is 38 b and for the second reaction it is 64 b. Corresponding resonance integral cross-sections in the epithermal region are 485 b and 2760 b, respectively.<sup>12</sup>

There are a few medically significant nuclides that can be produced in high specific activity by neutron capture reactions that produce an intermediate product that decays with relatively short half-life via beta decay to the desired product. An example is the production of Sc-47. This nuclide decays with half-life of 3.35 days. It emits a therapeutically significant beta particle along with a 159 keV photon that can be imaged. It can be produced by irradiating an enriched Ca-46 target in a thermal neutron flux. The Ca-47 produced by the <sup>46</sup>Ca(n, $\gamma$ ) reaction decays with a half-life of 4.54 days via beta-decay to Sc-47. The half-saturation yield is 11 mCi Sc-47/mg Ca-46 in a thermal neutron flux of  $1 \times 10^{14}$  ns<sup>-1</sup>cm<sup>-2</sup>.<sup>9</sup> If the target contains scandium impurity at a concentration of 1 ppm, the Sc-47 specific activity would be  $1.1 \times 10^7$  mCi/mg at the end of the irradiation.

Another important class of neutron reaction that occurs relatively efficiently in the epithermal flux of a nuclear reactor is inelastic neutron scatter. In this reaction the neutron interacts with the target nucleus, transferring sufficient energy to excite it to a metastable nuclear state that relaxes by emission of a gamma photon. This reaction is symbolized as (n,n' $\gamma$ ). An important therapeutic medical nuclide produced by this process is Sn-117m that decays with a 13.6 day half-life by isomeric transition with emission of Auger electrons and a 159 keV photon. It has been demonstrated that the yield of the <sup>117</sup>Sn(n,n' $\gamma$ )<sup>117m</sup>Sn reaction increases with the increase in epithermal neutron flux due to the strong neutron interaction resonances in the 4-125 eV energy range.<sup>13</sup>

A few medically significant radionuclides can be produced by (n,p) and (n, $\alpha$ ) reactions. Since the barrier to charged particle emission from an activated nucleus is high, neutrons of high energy (i.e. fast neutrons) must induce such reactions. This kind of process can explain, in part, the production of neutron-rich Cu-67 in a high-energy proton accelerator. Two reaction processes on naturally occurring zinc targets can explain the production of Cu-67. In a high energy proton beam (>100 MeV) there is a reasonable cross-section for the <sup>68</sup>Zn(p,2p)<sup>67</sup>Cu reaction,

explaining part of the Cu-67.<sup>14</sup> However, when targets are bombarded by high-energy protons, there is a large flux of mostly forward scattered neutrons generated during the spallation process. These neutrons will possess energies up to the energy of the bombarding protons. Such neutrons can induce the  $^{67}\text{Zn}(n,p)^{67}\text{Cu}$  reaction, and thus contribute to the overall Cu-67 yield in targets containing naturally-occurring zinc.<sup>15</sup> Naturally-occurring zinc is 18.8% Zn-68 and 4.1% Zn-67.<sup>2</sup> Note that enriched  $^{67}\text{Zn}$  targets might be used in the fast-flux regions of some nuclear reactors to produce  $^{67}\text{Cu}$  in relatively high specific activity by this latter reaction.

## Recovery and Purification of Radionuclides

### *Methods*

With few exceptions it is necessary to process the irradiated target material to recover, purify, and chemically convert the desired radionuclide for its end-use. Usually, one or more of the following techniques is used to accomplish the desired separation.<sup>16,17</sup>

- Ion Exchange
- Precipitation/Filtration
- Distillation or Sublimation
- Solvent or Solid Phase Extraction
- Electrolysis

The scope of this lesson prohibits a detailed discussion of the various recovery methods. However, it is important to provide a perspective on the significant considerations associated with producing a pure radionuclide tracer.

### *Chemistry and the Choice of Target Material*

Most commonly the first step of the process involves dissolution of target material. Obviously, the choice of the chemical and physical state of the target material significantly influences the ease with which the dissolution can proceed. Therefore, the choice of the target material should be made with an understanding of what will be required to dissolve the target. The dissolution will affect the chemical nature of both the target material and the element of the desired radionuclide, and influence the design of the ultimate chemical process. Generally, there are two major challenges for the chemist after the dissolution is accomplished. The first is to isolate the desired radionuclide from the bulk of the target material. The second is to complete a purification process that separates the desired element from radioactive and stable impurities that will adversely affect the ultimate applicability of the radionuclide product. It is relatively common practice for a procedure to be developed using unirradiated target material and appropriate tracers and analytical techniques to demonstrate the functionality of the process. Since the irradiation will sometimes significantly influence both the chemical and physical nature of the target, it will often be necessary to refine the separation process with actual irradiated targets.

### *Chemistry and Specific Activity*

An important consideration in developing the separation procedure is the specific activity of the product nuclide. Very often the final user desires the highest possible specific activity. Therefore, the chemist must be aware of the potential for contamination of the product with stable element of the desired radionuclide. Sources of contamination include the environment in which the process is performed and the reagents used to complete it. The magnitude of the concern is very dependent upon the element to which the desired nuclide belongs. For example, if the nuclide of interest is Cu-67, there are several potential sources of copper that one should avoid in the process environment. Also, one might use highly purified reagents that are very low in copper to accomplish the chemical procedure. If the desired nuclide is of a very rare element, for example Au-199, these concerns would be less significant.

It is important to note that in some instances it is necessary to actually add a "carrier" mass of the element of the desired nuclide to make the separation process work efficiently. For example, Se-75 is recovered from an aqueous solution of rubidium bromide by adding hydrazinium dihydrochloride to reduce the oxyanions of selenium to the element.<sup>18</sup> The selenium is then filtered from the solution. When this procedure is carried out without addition of carrier selenium, only about 20-30% of the Se-75 is recovered. If a few milligrams of sodium selenite is added to the solution before the reductive precipitation, then virtually 100% of the isotope is recovered. Sometimes, if this is necessary, and it is important not to compromise the specific activity, the chemist may be able to add a surrogate element that behaves chemically similarly to that of the desired nuclide. At some point later in

the process, the surrogate element should be separated from the product nuclide. As an example, tellurium behaves chemically like selenium in the reductive process described above, so a salt containing tellurium could be substituted for the sodium selenite prior to the reduction and separated electrochemically from the selenium after the filtration.<sup>17</sup>

After the purification process is completed, it is important to the end-user to know both the chemical speciation and the nature of the chemical matrix in which the nuclide exists. Since the product is often used to label a compound or to load a generator, knowledge of the chemical form is essential to assure the performance of the nuclide in its final application. For some elements this is not a difficult issue because the speciation is well defined and easily controlled by the final matrix. However, for other elements, the final solution matrix and its storage can dramatically affect oxidation states, ionic form, and physical phase of the product nuclide. For some applications, it is important to provide the product free of pyrogens and potential infectants. Under such circumstances, it may be that the whole process must be done in accordance with current Good Manufacturing Practices (cGMP). This would significantly influence the nature of the process and the facilities in which it is done.

### *Facilities for Target Processing*

When the irradiation is completed, the target material and whatever encapsulation has been used to contain it will be very radioactive. Depending upon the type and length of irradiation, the target will be sufficiently radioactive to provide a lethal dose of radiation within a very short time of personnel exposure. The target must be carefully retrieved and transferred to a sufficiently shielded facility to safely handle the material during the process. The process must either be automated so that it can proceed with minimal human exposure, or must be performed using well-engineered remote manipulations in a hot-cell facility. Such facilities are very expensive to build and maintain, and require well-trained personnel to work in them.<sup>16,19</sup> Figure 6 shows a photograph of a hot-cell facility used to process targets irradiated in a high energy, high current accelerator to produce nuclides by spallation reactions. Such targets are relatively massive (up to several hundred grams) and are highly radioactive. Extensive shielding is required. Similar facilities are required to process uranium targets for Mo-99. Figure 7 is a photograph of a hot-cell facility used to process targets that have been irradiated in a lower energy cyclotron. These targets usually weigh only a few grams and are significantly less radioactive, thus requiring less massive hot-cells for processing.

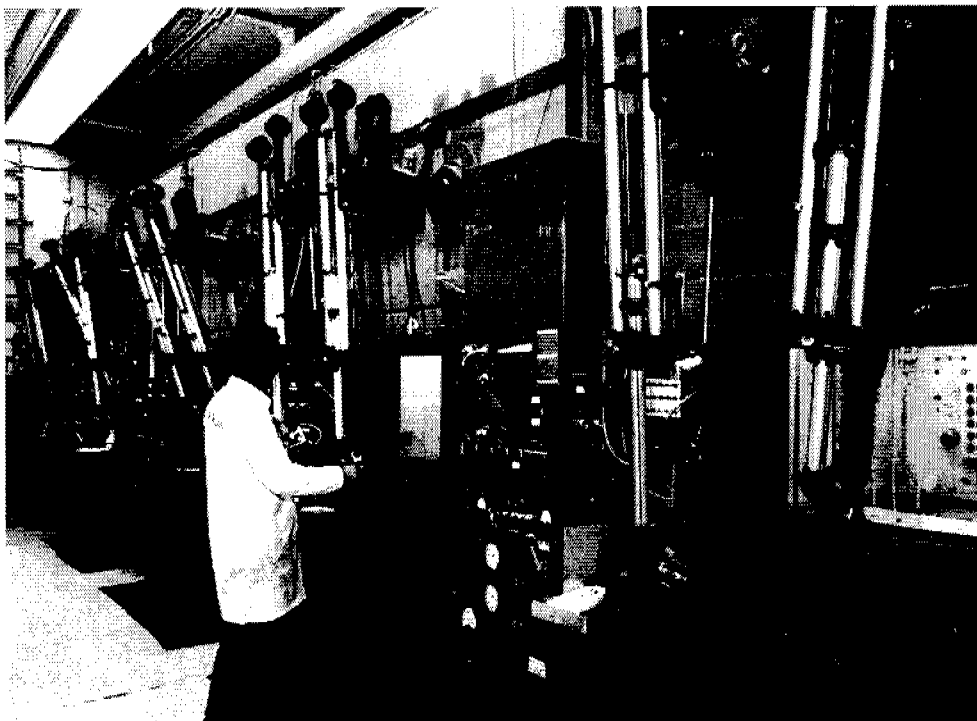


Figure 6. Hot Cell facility used to recover spallation produced radionuclides.



Figure 7. Hot Cell facility used to recover radioisotopes from cyclotron irradiated targets.

It is becoming increasingly important to carefully consider the type and volume of the waste-stream that emerges from any chemical process for nuclide recovery and purification. Procedures should be designed to minimize the amount of mixed waste (hazardous chemicals mixed with radioactive materials) generated.<sup>20</sup> The optimum facility has certified liquid and solid waste handling facilities and storage or disposal capability on site. Otherwise, waste must be transported, at substantial cost, to approved radioactive storage and disposal sites that are becoming increasingly difficult to find.

### PRODUCTION OF Mo-99 FOR THE Mo-99/Tc-99m GENERATOR

This lesson concludes with a discussion of the various ways that Mo-99 might be produced. This example was chosen because it is accessible by both reactor and accelerator production, and it is possibly the most significant clinical medical radionuclide. At the beginning of 1990 the world-wide demand for Mo-99 to support the Tc-99m generator was about 16,000 Ci/week at time of receipt by pharmaceutical companies.<sup>22</sup> If it is assumed that about 1.5 days elapse from the end of irradiation to delivery, about 22,000 Ci/week must be produced at the end of irradiation. The demand for the nuclide has grown significantly since that time, with the current U.S. demand alone reaching about 20,000 Ci/week.<sup>23</sup> In order to support the manifold of imaging pharmaceuticals based upon Tc-99m, this supply must be regular and dependable.

#### Reactor Production

All of the Mo-99 generators used in the United States and most of those in the rest of the world depend upon Mo-99 produced via the  $^{235}\text{U}(n,f)^{99}\text{Mo}$  reaction. The fission yield of Mo-99 on  $^{235}\text{U}$  is 6.133%.<sup>2</sup> A seven day irradiation in a thermal neutron flux of  $1 \times 10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$  will produce about 200 Curies per gram of  $^{235}\text{U}$ .<sup>23</sup> The specific activity of Mo-99 produced by this reaction is approximately 5000 Ci Mo-99/g Mo at the end of the irradiation. This is about an order of magnitude less than the theoretical maximum specific activity. There are three stable isotopes of Mo produced at relatively high yield during the irradiation that reduce the specific activity. These are Mo-97 (5.9% fission yield), Mo-98 (5.9%) and Mo-100 (6.3%). The generator manufacturers generally calibrate the generators on the basis of "6-day Curies." Since the half-life of Mo-99 is 2.75 days, the specific activity of fission-produced Mo-99 at 6 days after bombardment is about 1100 Ci/g. It is this high specific activity

that makes fission-produced Mo-99 preferable to generator manufacturers. With higher specific activity, less support material is required in the generator to avoid breakthrough of the Mo-99 parent during generator elution.

There are some problems with using the fission process to produce Mo-99. Since only about 6% of the fission reactions yield the desired nuclide, there are many other fission radionuclides produced during the irradiation.<sup>3</sup> These nuclides add substantially to the radiation field, and for the most part, simply become part of the waste stream. Elaborate hot-cell facilities and substantial expertise are required for processing the fission-produced material and for storing and packaging the waste. It is worth noting that some production facilities recover some other important fission nuclides such as I-131, Xe-133, Ru-103, Sm-153, Sr-89, and a few others.<sup>24</sup> A great deal of care must be taken in the chemical processing of the uranium to exclude toxic alpha emitting contaminants from the Mo-99 product. Especially problematic is Pu-239 which is produced via the  $^{238}\text{U}(n,\gamma)^{239}\text{U} \rightarrow ^{239}\text{Np} \rightarrow ^{239}\text{Pu}$  reaction cascade. Naturally occurring uranium is only 0.72%  $^{235}\text{U}$  and 99.27%  $^{238}\text{U}$ . Even if the target material is enriched to 93%  $^{235}\text{U}$ , a substantial amount of  $^{238}\text{U}$  would be available for production of  $^{239}\text{Pu}$ .<sup>23</sup>

An alternative approach for reactor production is to use the  $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$  reaction.<sup>23</sup> The thermal neutron capture cross-section for this reaction is 0.14 b. Based upon this cross-section, neglecting burn-up, a 1 gram Mo-98 target would give a half-saturation yield of about 16 Ci of Mo-99 if irradiated in a thermal neutron flux of  $1 \times 10^{15} \text{ n cm}^{-2} \text{ s}^{-1}$  (an order of magnitude higher than in the above case for fission production). It is evident that both the yield and the specific activity are significantly lower than for the fission-produced Mo-99. The reduced yield can be partially offset by using larger masses of target material, though this does not improve the specific activity. If specific activity is not a significant issue, as is the case with some generator systems, there are some other advantages to (n, $\gamma$ ) produced Mo-99 over fission-produced material. Very little post-irradiation processing is required for (n, $\gamma$ ) Mo-99, thus substantially minimizing the amount of waste relative to fission product. It is important to note that molybdenum target material for (n, $\gamma$ ) production of Mo-99 should be of high purity. Certain impurities in molybdenum compounds can capture neutrons, giving rise to undesirable (n, $\gamma$ ) products. Rhenium is a common impurity in molybdenum, and if present will give rise during irradiation to  $^{188}\text{Re}$  and  $^{186}\text{Re}$  that are not easily separated from the molybdenum. Despite some of the attractive features of this production mode, it is unlikely that it will become significant as long as reliable supply of high specific activity fission product is available.

### Accelerator Production

Both of the Mo-99 production modalities discussed above depend upon nuclear reactors as a neutron source. Some researchers have investigated production of Mo-99 and direct production of Tc-99m by particle accelerators as an alternative source of supply.<sup>25</sup> The  $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ ,  $^{100}\text{Mo}(p,pn)^{99}\text{Mo}$ , and  $^{100}\text{Mo}(p,2p)^{99m}\text{Nb} \rightarrow ^{99}\text{Mo}$  reactions were studied by irradiation of natural molybdenum metal foil targets in the proton energy range from 68 MeV down to 8 MeV. The respective Q values for these reactions are -7.9 MeV, -8.3 MeV and -11.1 MeV. Extrapolating the results to irradiation of 97% enriched  $^{100}\text{Mo}$  targets, the researchers concluded that about 2 Ci/hr of Mo-99 could be produced on two 5 gram targets irradiated simultaneously in a dual beam 70 MeV cyclotron with 200  $\mu\text{A}$  current on each target. The Mo-99 produced in this way would have a specific activity of about 50 Ci/g at end of bombardment. Clearly, neither the yield nor the specific activity is competitive with fission-produced Mo-99. However, during the irradiation of these Mo-100 targets,  $^{99m}\text{Tc}$  would simultaneously be produced at a yield of about 40 Ci/h. The investigators correctly reasoned that many economic, logistical, legal, environmental, and social factors would need to be considered to evaluate whether accelerator supplied  $^{99m}\text{Tc}$ , both directly and through  $^{99}\text{Mo}/^{99m}\text{Tc}$  generators, would be feasible. Assume a scenario for a supply system by this route in the United States. The current U.S. demand for Mo-99 for generators is about 13.6 kCi per week, calibrated at time of receipt by the pharmaceutical company. About 200 Ci/week of accelerator-produced Mo-99 could be delivered to the pharmaceutical companies for generator production if each day a 16 hour irradiation were performed with 6 hours allotted for processing and shipping. Clearly, this is not a significant fraction of the full demand. However, consider that at the same time about 600 Ci Tc-99m/day, or 4000 Ci Tc-99m/week, could be distributed to pharmaceutical sites within about a few hour radius of the cyclotron. If several such facilities were placed strategically around the United States, it is not unreasonable to assume that a significant fraction of the U. S. demand for Tc-99m could be met.

Is such a scenario really reasonable? Based upon current prices for the bulk Mo-99, and assuming that at least half of the market share in the U.S. were supplied by this route, several 10's of millions of dollars per year of gross revenue would be generated. However, to meet the demand, 5 to 10 sites strategically located around the country would be required. A capital investment of \$25-40 Million per site would be necessary for construction and start-up. Though this is a large sum of money, it is favorable in comparison to construction of a new reactor and the

supporting infrastructure for fission-produced Mo-99. In view of environmental and safety concerns associated with nuclear reactor facilities, the general public would likely be more accepting of accelerator facilities. Obviously, many issues would have to be addressed to assure a reliable supply of Tc-99m from multiple accelerators, so it appears highly unlikely that this mode of supply would be developed in nations such as the U.S. which have reliable access to fission-produced Mo-99. However, one could imagine that this accelerator technology might support expansion of modern nuclear medicine into developing regions of the world.

Scientists are also investigating another mechanism by which proton accelerators might be used to produce Mo-99. The Department of Energy is evaluating the feasibility of using a very high-energy, high-current proton accelerator as a source of neutrons. This premise is based upon the understanding that during spallation processes on nuclei of high-mass targets (e.g. tungsten) a high flux of secondary neutrons is produced. These high-energy neutrons can, in principal, be thermalized in a system designed to contain  $^{235}\text{U}$  targets for fission production of Mo-99 and other medical radionuclides. It remains to be seen whether such a concept is technically and economically viable as an alternative to reactor production.

## CONCLUSION

The intent of this lesson has been to give the reader an understanding of the many difficult factors that must be considered and implemented to provide radionuclides for the practice and development of nuclear medicine. The choice of the best mode of production is complicated by many factors. Nuclear reaction physics will sometimes limit production to either a reactor neutron irradiation or accelerator beam bombardment. Some nuclides might be produced by either irradiation mode, but economics, politics, regulatory concerns and availability of facilities may dictate which mode is ultimately used. As a general rule, with definite exceptions, reactor production is favorable for neutron-rich nuclides. These nuclides have an excess of neutrons relative to the stable nuclides of the element and decay predominantly by beta-decay. Such nuclides are often effective for labeling of therapeutic compounds. Again with exceptions, neutron-poor nuclides are produced in particle accelerators. Since these nuclides contain a deficit of neutrons relative to the stable nuclides of the element, they decay either by positron emission or electron-capture. The positron-emitters have potential for PET imaging applications. Nuclides decaying by electron-capture often emit lower-energy photons and conversion electrons making them potentially valuable for both imaging and therapy. Nuclides produced in a particle accelerator can often be produced in very high specific-activity since the targets frequently contain a different element than the desired nuclide. Table 1 lists a variety of nuclides produced by particle accelerators showing some production modes and medical application of the radionuclide. Table 2 is a similar table for neutron produced nuclides. The interested reader can find detailed information about the production of these and other radionuclides in the literature.<sup>9,24-34</sup>

At any production facility, expertise in chemistry, physics, and engineering, along with skilled technical personnel are essential. The work must be done with a clear understanding of regulations and requirements associated with safely operating nuclear facilities, and storing and transporting hazardous radioactive materials. Without the reliable operation of complex production facilities, the practice of nuclear medicine would not be possible.

Table 1. Some significant accelerator produced medical radionuclides.

Nuclide	Practical Production Reactions	Applications
$^{11}\text{C}$	$^{10}\text{B}(\text{d},\text{n}); ^{11}\text{B}(\text{p},\text{n}); ^{14}\text{N}(\text{p},\alpha); ^{12}\text{C}(\text{p},\text{pn})$	Positron Emission Tomography, Receptor R&D
$^{13}\text{N}$	$^{12}\text{C}(\text{d},\text{n}); ^{13}\text{C}(\text{p},\text{n}); ^{16}\text{O}(\text{p},\alpha)$	Positron Emission Tomography, Receptor R&D
$^{15}\text{O}$	$^{14}\text{N}(\text{d},\text{n}); ^{12}\text{C}(\alpha,\text{n}); ^{16}\text{O}(\text{He},\alpha)$	Positron Emission Tomography, R&D
$^{18}\text{F}$	$^{18}\text{O}(\text{p},\text{n}); ^{20}\text{Ne}(\text{d},\alpha); ^{19}\text{F}(\text{p},\text{pn}); ^{15}\text{O}(\alpha,\text{pn})$	Positron Emission Tomography, Metabolic and receptor Brain Imaging, receptor R&D
$^{32}\text{P}$	$\text{KCl}(\text{p},\text{spall})$	Treatment of polycythemia vera, Biomedical R&D
$^{33}\text{P}$	$\text{KCl}(\text{p},\text{spall})$	Biomedical R&D
$^{67}\text{Cu}$	$^{\text{nat}}\text{Zn}(\text{p},\text{spall}); ^{\text{nat}}\text{Zn}(\text{p},\text{xn}); ^{70}\text{Zn}(\text{p},\alpha);$	Lymphoma tumor imaging and therapy R&D
$^{67}\text{Ga}$	$^{\text{Nat}}\text{Zn}(\text{p},\text{xn}); ^{66}\text{Zn}(\text{d},\text{n}); ^{67}\text{Zn}(\text{p},\text{n}); ^{68}\text{Zn}(\text{p},2\text{n}); ^{\text{nat}}\text{Zn}(\alpha,\text{x}); ^{65}\text{Cu}(\alpha,2\text{n}); \text{RbBr}(\text{p},\text{spall}); \text{GaAs}(\text{p},\text{spall})$	Study and treatment of tumor and inflammatory diseases
$^{68}\text{Ge}$	$^{\text{nat}}\text{RbBr}(\text{p},\text{spall}); ^{69}\text{Ga}(\text{p},2\text{n}); ^{66}\text{Zn}(\alpha,2\text{n})$	Parent of $^{68}\text{Ge}/^{68}\text{Ga}$ generator; $^{68}\text{Ga}$ used for PET Tumor imaging; Used to manufacture calibration sources for PET cameras
$^{72}\text{Se}$	$\text{RbBr}(\text{spall}); ^{75}\text{As}(\text{p},4\text{n})$	Parent of $^{72}\text{Se}/^{72}\text{As}$ generator; $^{72}\text{As}$ used in R&D on various imaging and therapeutic oncological applications
$^{81}\text{Rb}$	$^{\text{Nat}}\text{Kr}(\text{p},\text{xn}); ^{82}\text{Kr}(\text{p},2\text{n}); ^{82}\text{Kr}(\text{d},3\text{n}); ^{85}\text{Rb}(\text{p},5\text{n}) ^{81}\text{Sr} \rightarrow ^{81}\text{Rb}$	Parent of $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ generator for SPECT pulmonary ventilation, organ perfusion
$^{82}\text{Sr}$	$^{\text{Nat}}\text{Mo}(\text{p},\text{spall}); ^{\text{nat}}\text{Rb}(\text{p},\text{xn}); ^{82}\text{Kr}(\text{He},3\text{n})$	Parent of $^{82}\text{Sr}/^{82}\text{Rb}$ generator for myocardial perfusion imaging
$^{99}\text{Mo}$ ( $^{99\text{m}}\text{Tc}$ )	$^{100}\text{Mo}(\text{p},2\text{p}) ^{99\text{m}}\text{Nb} \rightarrow ^{99}\text{Mo} ^{100}\text{Mo}(\text{p},\text{pn}) ^{99\text{m}}\text{Tc}$	Numerous diagnostic procedures based upon $^{99\text{m}}\text{Tc}$ radiopharmaceuticals
$^{103}\text{Pd}$	$^{103}\text{Rh}(\text{p},\text{n}); ^{\text{nat}}\text{Ag}(\text{p},\text{X})$	Prostate cancer treatment
$^{111}\text{In}$	$^{110}\text{Cd}(\text{d},\text{n}); ^{111}\text{Cd}(\text{p},\text{n}); ^{112}\text{Cd}(\text{p},2\text{n}); ^{109}\text{Ag}(\alpha,2\text{n}); ^{\text{nat}}\text{In}(\text{p},\text{xn}) ^{111}\text{Sn} \rightarrow ^{111}\text{In}$	Oncological, CNS, Blood Cell scintigraphy
$^{123}\text{I}$	$^{123}\text{Te}(\text{p},\text{n}); ^{122}\text{Te}(\text{d},2\text{n}); ^{124}\text{Te}(\text{p},2\text{n}); ^{123}\text{Sb}(\text{He},3\text{n}); ^{121}\text{Sb}(\alpha,2\text{n}); ^{124}\text{Xe}(\text{p},\text{X}); ^{127}\text{I}(\text{p},5\text{n}) ^{123}\text{Xe} \rightarrow ^{123}\text{I};$	Scintigraphy for thyroid function, kidney function and cerebral blood flow
$^{127}\text{Xe}$	$^{127}\text{I}(\text{p},\text{n}); ^{127}\text{I}(\text{d},2\text{n}); ^{\text{nat}}\text{CsCl}(\text{spall}); ^{\text{nat}}\text{CsF}(\text{spall})$	Scintigraphy for pulmonary ventilation and cerebral blood flow
$^{201}\text{Tl}$	$^{203}\text{Tl}(\text{p},3\text{n}) ^{201}\text{Pb} \rightarrow ^{201}\text{Tl}; ^{199}\text{Hg}(\text{d},2\text{n})$	Myocardial perfusion imaging

Table 2. Some significant reactor produced radionuclides.

Nuclide	Practical Production Reactions	Applications
$^{47}\text{Sc}$ ( $^{47}\text{Ca}$ )	$^{47}\text{Ti}(n,p)$ ; $^{46}\text{Ca}(n,\gamma)^{47}\text{Ca} \rightarrow ^{47}\text{Sc}$	Biomedical R&D; PET R&D ( $^{47}\text{Ca}$ used to investigate gastro-intestinal absorption and metabolism)
$^{60}\text{Co}$	$^{59}\text{Co}(n,\gamma)$	Teletherapy
$^{64}\text{Cu}$	$^{63}\text{Cu}(n,g)$ ; $^{64}\text{Zn}(n,p)$	Oncological PET imaging and therapy
$^{67}\text{Cu}$	$^{67}\text{Zn}(n,p)$ ;	Oncological imaging and therapy
$^{89}\text{Sr}$	$^{88}\text{Sr}(n,\gamma)$	Bone pain palliation
$^{90}\text{Sr}$ ( $^{90}\text{Y}$ )	$^{233,235,238}\text{U}(n,f)$ ; $^{239,241}\text{Pu}(n,f)$	Parent of $^{90}\text{Y}$ used in treatment of chronic synovitis and other joint problems; Used in R&D for immunotherapy
$^{99}\text{Mo}$ ( $^{99\text{m}}\text{Tc}$ )	$^{233,235,238}\text{U}(n,f)$ ; $^{98}\text{Mo}(n,\gamma)$ ; $^{100}\text{Mo}(p,2p)^{99\text{m}}\text{Nb} \rightarrow ^{99}\text{Mo}$	Numerous diagnostic procedures based upon $^{99\text{m}}\text{Tc}$ radiopharmaceuticals
$^{103}\text{Pd}$	$^{102}\text{Pd}(n,\gamma)$	Prostate cancer treatment
$^{117\text{m}}\text{Sn}$	$^{116}\text{Sn}(n,\gamma)$ ; $^{117}\text{Sn}(n,n'\gamma)$	Bone pain palliation
$^{125}\text{I}$	$^{124}\text{Xe}(n,\gamma)^{125}\text{Xe} \rightarrow ^{125}\text{I}$	Renal function measurements; Detection of osteoporosis; Treatment of prostate cancer; R&D in radioimmunotherapy
$^{127}\text{Xe}$	$^{126}\text{Xe}(n,\gamma)$	Scintigraphy for pulmonary ventilation and cerebral blood flow
$^{131}\text{I}$	$^{235}\text{U}(n,f)$ ; $^{130}\text{Te}(n,\gamma)^{131}\text{Te} \rightarrow ^{131}\text{I}$	Thyroid imaging; Treatment of hyperthyroidism; Treatment of Lymphoid tissue tumors; R&D in radioimmunotherapy
$^{153}\text{Sm}$	$^{152}\text{Sm}(n,\gamma)$	Bone pain palliation; Brain cancer treatment
$^{186}\text{Re}$	$^{185}\text{Re}(n,\gamma)$	R&D in radioimmunotherapy; Bone pain palliation
$^{188}\text{W}$ ( $^{188}\text{Re}$ )	$^{186}\text{W}(2n,\gamma)$	$^{188}\text{W}$ is the parent for $^{188}\text{Re}$ generator used in R&D in radioimmunotherapy
$^{192}\text{Ir}$	$^{191}\text{Ir}(n,\gamma)$	R&D in brachytherapy to prevent restenosis

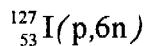


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## QUESTIONS

1. What is the product nuclide if a target containing I-127 is bombarded with protons of sufficient energy to cause the following reaction?



- a. Xe-128 (atomic number 54)  
b. Xe-122 (atomic number 54)  
c. I-121 (atomic number 53)  
d. I-128 (atomic number 53)
2. What particle is ejected if a deuteron reacts with a Sr-86 nucleus to produce Y-87? The atomic number of Sr is 38. The atomic number of Y is 39.
- a. proton  
b. neutron  
c. alpha  
d. gamma photon
3. Given the following mass data, what is the Q value for the reaction  ${}^{63}\text{Cu}(p,2n){}^{62}\text{Zn}$ ?  
 ${}^{63}\text{Cu} = 62.9296$  amu  
 ${}^{62}\text{Zn} = 61.9291$  amu  
proton = 1.0078 amu  
neutron = 1.0086 amu
- a. -8.29 MeV  
b. +8.29 MeV  
c. -93.1 MeV  
d. +93.1 MeV
4. Naturally occurring copper is 69.17%  ${}^{63}\text{Cu}$  and 30.83%  ${}^{65}\text{Cu}$ . Which one of the following target masses would produce the greatest amount of  ${}^{62}\text{Zn}$  via the  ${}^{63}\text{Cu}(p,2n)$  reaction, assuming that each target was fabricated and irradiated identically?
- a. 650 mg of natural copper metal  
b. 600 mg of copper enriched to 70%  ${}^{63}\text{Cu}$   
c. 375 mg of copper enriched to 92%  ${}^{63}\text{Cu}$   
d. 475 mg of copper enriched to 98%  ${}^{63}\text{Cu}$
5. The cross section for the  ${}^{63}\text{Cu}(p,2n){}^{62}\text{Zn}$  reaction using 20 MeV protons is 28 mb. A thin target of 98.6% enriched  ${}^{63}\text{Cu}$ , having a thickness of 7.5 mg/cm<sup>2</sup>, was irradiated for 6 minutes with a 10 microampere current of 20 MeV protons. How many millicuries of  ${}^{62}\text{Zn}$  would be present in the target at the end of irradiation? (Note: Zn-62 = 62.9296 amu; 1 mCi =  $2.22 \times 10^9$  disintegrations per minute; half-life of  ${}^{62}\text{Zn} = 9.1$  hours)
- a. 0.056 mCi  
b. 20 mCi  
c. 0.025 mCi  
d. 1.5 mCi
6. Which one of the following statements is not true concerning the beam during irradiation of a thick target by an incident beam of 20 MeV protons?
- a. The average energy of the protons will decrease as the beam traverses the target.  
b. The average intensity (protons per second) of the beam will decrease as the beam traverses the target.  
c. The cross-sectional area of the beam will decrease as the beam traverses the target.  
d. The temperature of the target will increase during the course of the irradiation.

7. Which one of the following particles cannot be accelerated in a linac or cyclotron?
- alpha particle
  - deuteron
  - proton
  - neutron
8. An assembly of fissionable fuel will only sustain a nuclear chain reaction when which one of the following necessary conditions is met?
- The mass of the fuel is large.
  - The temperature of the assembly is raised.
  - At least one neutron in each fission reaction in the assembly induces a fission reaction in another nucleus.
  - The multiplication factor,  $k$ , for the assembly is less than 1.
9. The compound nucleus mechanistic model best explains the distribution of products in which type of nuclear reaction?
- $(n,\gamma)$
  - spallation
  - $(p,4n)$
  - $(n,\text{fission})$
10. Which one of the following nuclear reaction processes will produce the greatest number of different nuclides?
- $(n,\gamma)$
  - $(2n,\gamma)$
  - $(n,n'\gamma)$
  - $(n,\text{fission})$
11. Which one of the following nuclear reactions will only occur at neutron energies in excess of thermal levels?
- $(n,\gamma)$
  - $(n,p)$
  - $(n,\text{fission})$
  - $(2n,\gamma)$
12. Ruthenium-97 (half-life = 2.9 days) can be produced in a nuclear reactor via the  $^{96}\text{Ru}(n,\gamma)$  reaction. Which one of the following changes would not increase the yield of  $^{97}\text{Ru}$ ? Assume that everything but the stated change remains the same between in each case.
- Irradiate a 1 gram target of natural ruthenium (5.54%  $^{96}\text{Ru}$ ) in thermal neutron flux of  $1.0 \times 10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$  rather than in a thermal neutron flux of  $5 \times 10^{13} \text{ n cm}^{-2} \text{ s}^{-1}$ .
  - Irradiate a 1 gram target of natural ruthenium rather than a 0.5 gram target.
  - Irradiate a 1 gram ruthenium target that has been enriched to 90%  $^{96}\text{Ru}$  rather than a 2 gram target of natural ruthenium.
  - Irradiate a 1 gram ruthenium target that has been enriched to 90%  $^{96}\text{Ru}$  for 2.0 days rather than 2.9 days.
13. Which of the following changes would not increase the specific activity of the  $^{97}\text{Ru}$  product from the  $^{96}\text{Ru}(n,\gamma)$  reaction? Assume that everything but the stated change remains the same in each case.
- Irradiate a 1 gram target of natural ruthenium (5.54%  $^{96}\text{Ru}$ ) in thermal neutron flux of  $1.0 \times 10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$  rather than in a thermal neutron flux of  $5 \times 10^{13} \text{ n cm}^{-2} \text{ s}^{-1}$ .
  - Irradiate a 1 gram target of natural ruthenium rather than a 0.5 gram target.
  - Irradiate a 1 gram ruthenium target that has been enriched to 90%  $^{96}\text{Ru}$  rather than a 2 gram target of natural ruthenium.
  - Irradiate a 90% enriched  $^{96}\text{Ru}$  target in the epithermal region of the reactor where strong resonance reactions occur.

14. Specific activity of a recovered radionuclide is defined as:
- the amount of radioactivity from the nuclide at a specific time after completion of the recovery process.
  - the radioactivity from the nuclide expressed as the number of millicuries per milliliter of solution.
  - the ratio of the radioactivity from the nuclide to the mass of element to which the nuclide belongs.
  - the ratio of the radioactivity from the nuclide to the radioactivity from all other radionuclide impurities.
15. Which item below will not improve the specific activity of a product radionuclide produced via a (p,n) reaction?
- Use ultrapure target material that does not contain as impurity the element to which the product nuclide belongs.
  - Use ultrapure reagents that do not contain as impurity the element to which the product nuclide belongs in the chemical recovery process
  - Use a carrier mass of the element to which the product nuclide belongs in the chemical recovery process.
  - Perform the process in an environment that does not contain sources of the element to which the product nuclide belongs.
16. Which target would most likely require the greatest amount of shielding to protect the processing personnel?
- 5 grams of  $^{152}\text{Sm}$  irradiated to produce  $^{153}\text{Sm}$  via the (n, $\gamma$ ) process.
  - 5 grams of  $^{235}\text{U}$  irradiated to produce  $^{99}\text{Mo}$  via the (n,fission) process.
  - 5 grams of natural Rb irradiated to produce  $^{82}\text{Sr}$  via the (p,xn) process.
  - 5 grams of  $^{70}\text{Ge}$  irradiated to produce  $^{72}\text{Se}$  via the  $^{70}\text{Ge}(\alpha,2n)$  reaction.
17. The end-user of a radionuclide generally will need to know all of the following about the product except:
- the exact chemical nature (e.g. oxidation state, chemical matrix) of the nuclide.
  - the specific activity of the nuclide.
  - the concentration of the radioactivity from the nuclide in the product solution.
  - the precise nuclear reaction by which the nuclide was produced.
18. Which statement most accurately completes the following sentence? Proton spallation
- produces many different nuclides in the target.
  - produces nuclides that are generally neutron rich.
  - results in targets that are easy to process.
  - requires low-energy (less than 20 MeV) incident protons.
19. Which of the following changes would least likely alter the yield when producing a nuclide via the (n, $\gamma$ ) reaction? (Assume all else remains the same in each case.)
- Increase the mass of the target nuclide.
  - Change the chemical form of the target nuclide.
  - Decrease the enrichment of the target nuclide.
  - Increase the neutron flux of the irradiation.
20. Which component is found in a cyclotron but not a linac?
- ion source
  - rf generator
  - drift tubes
  - electromagnet
21. Which component of an ideally operating accelerator predominantly determines the beam intensity (particles accelerated per second)?
- the out put of the ion source
  - the gap potential
  - the length of the accelerator
  - the strength of the magnetic field

22. This question refers to Figure 4 of the lesson. The broad peak centered at mass number ~90 on the curve for 400 MeV proton irradiation of Bi-209 is due primarily to:
- spallation processes.
  - simple compound nucleus processes.
  - (p, $\gamma$ ) reaction processes.
  - proton induced fission processes.
23. An important advantage to production of  $^{99}\text{Mo}$  via the  $^{235}\text{U}(\text{n},\text{f})$  reaction is:
- product of high specific activity.
  - ease of process to recover  $^{99}\text{Mo}$ .
  - low amounts of radioactive waste produced
  - target material readily and cheaply available.
24. An important advantage to production of  $^{99}\text{Mo}$  via the  $^{98}\text{Mo}(\text{n},\gamma)$  reaction is:
- product of high specific activity.
  - high yield relative to fission production.
  - relative ease of process to recover  $^{99}\text{Mo}$ .
  - $^{188}\text{Re}$ ,  $^{186}\text{Re}$  are valuable by-products.
25. Which one of the following reaction processes is not used for production of  $^{99}\text{Mo}$ ?
- (n, $\gamma$ )
  - (n,f)
  - (n,p)
  - (p,2p)





