

## PRODUCTION CONSIDERATIONS FOR THE "CLASSICAL" PET NUCLIDES

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### I. INTRODUCTION

Coupled with the advancement in non-invasive cross-sectional imaging techniques for identification of structural alterations in diseased tissues, there have been significant advances in the development of *in vivo* methods for quantifying functional metabolism in both normal and diseased tissues. Positron emission tomography (PET) is an example of such a technique that has been shown to yield the physiologic information necessary for clinical diagnoses based upon altered tissue metabolism.

One of the most widely recognized advantages of positron emission tomography is the use of the positron-emitting biologic radiotracers (C-11, O-15, N-13, F-18) that mimic natural substrates. These radionuclides have well documented nuclear reaction cross sections appropriate for "baby" cyclotron energies and the corresponding "hot atom" target chemistries are reasonably well understood. There does however, exist a disadvantage in that these biologic radionuclides possess relatively short half-lives and are therefore, unable to be transported to sites at great distances from the production facility.

Currently there are three PET drugs officially recognized by the U.S. Food and Drug Administration. They are: Sodium fluoride F-18 injection, Rubidium chloride-82 injection and Fludeoxyglucose (FDG) F-18 injection. In 1972, sodium fluoride F-18 (NDA 17-042) was approved as a new drug application for bone imaging to define areas of altered osteogenic activity but the manufacturer ceased marketing this product in 1975. Rubidium chloride 82 injection (NDA 19-414) was approved in 1989 indicated for assessment of regional myocardial perfusion in the diagnosis and localization of myocardial infarction. Most recently, fludeoxyglucose (FDG) F-18 injection (NDA 20-306) was recognized in 1994 for identification of regions of abnormal glucose metabolism initially associated with foci of epileptic seizures but currently recognized in its application to various metastatic diseases (Dotzel 2000).

Over the past few decades, PET studies with radiolabeled drugs have provided new information on drug uptake, distribution, and the kinetic relationships. A recent critique on the design and development of PET radiopharmaceuticals has been published (Crouzel et al. 1993) as well as several articles involving the future of PET in drug research and development and the production targetry available from various manufacturers of cyclotrons (Satyamurthy et al. 1999).

The increasing amount of clinically relevant information being obtained with PET has generated a demand for new routes for the widespread and cost-effective generation of the biologic radionuclides and their incorporation into appropriate radiopharmaceuticals.

## II. PRODUCTION

### Definition of Nuclear Reaction Cross-section

A nuclear reaction is one in which a nuclear particle is absorbed into a target nucleus, resulting in a very short-lived compound nucleus. This excited nucleus will decompose along several pathways to products. There are a wide variety of nuclear reactions that are used in an accelerator to produce artificial radioactivity. The bombarding particles are usually protons, deuterons, or helium particles. The energies used range from a few MeV to hundreds of MeV. One of the most useful models for nuclear reactions is the compound nucleus model originally introduced by Bohr in 1936. In this model, the incident particle is absorbed into the nucleus of the target material and the energy is distributed throughout the compound nucleus. In essence the nucleus comes to some form of equilibrium before decomposing with the emission of particles. These two steps are considered to be independent of one another. It doesn't matter how the compound nucleus got to the high-energy state, the evaporation of the particles will be independent of the way in which it was formed. The total amount of excitation energy contained in the nucleus will be given by the equation:

$$U = \frac{M_A}{M_A + M_a} T_a + S_a$$

Where:

U = Excitation Energy

$M_A$  = mass of the target nucleus

$M_a$  = mass of the incident particle

$T_a$  = kinetic energy of the incident particle

$S_a$  = binding energy of the incident particle in the compound nucleus

These nucleus can decompose along several channels as shown here in Figure 1:

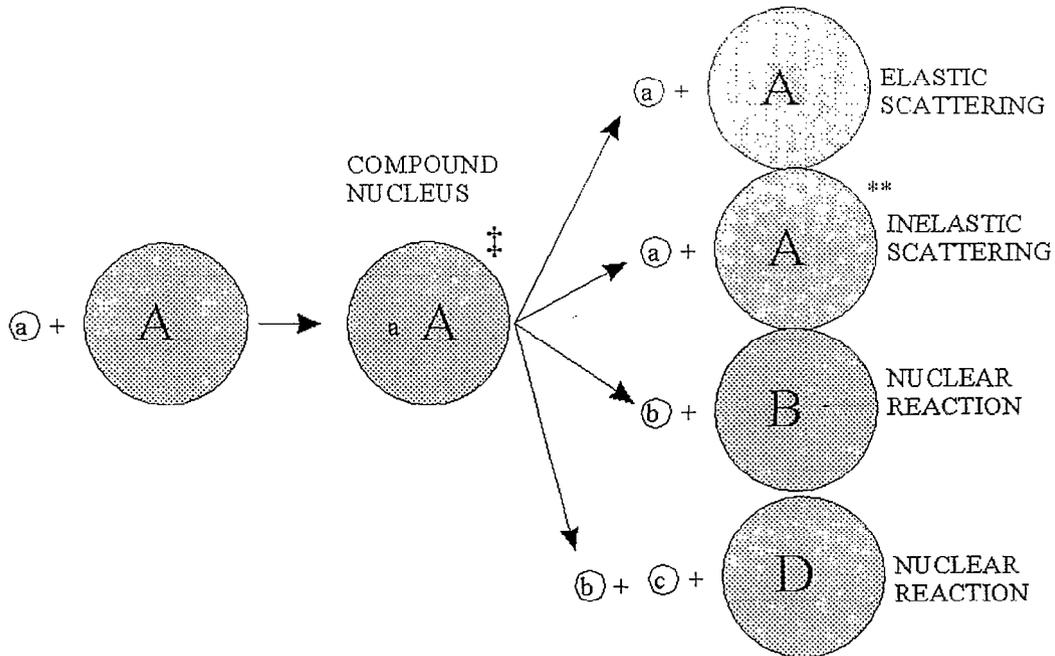


Figure 1 – Formation and disintegration of the compound nucleus

When the compound nucleus decomposes, the kinetic energy of all the products may be either greater or less than the total kinetic energy of all the reactants. If the energy of the products is greater, then the reaction is said to be exoergic. If the kinetic energy of the products is less than the reactants, then the reaction is endoergic. The magnitude of this difference is called the Q value. If the reaction is exoergic, Q values are positive. An energy level diagram of a typical reaction is shown in Figure 2.

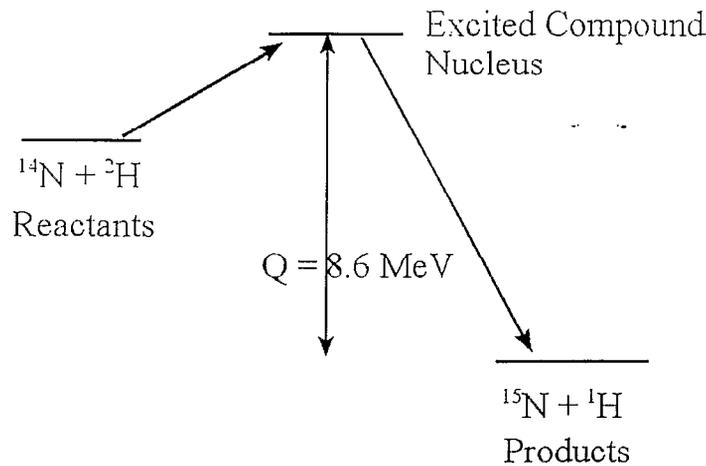


Figure 2 Energy level diagram for a nuclear reaction. The Q-value is the difference in the energy levels of the reactants and the products

The nuclear reaction cross-section represents the total probability that a compound nucleus will be formed and that it will decompose in a particular channel. There is a minimum energy below which a nuclear reaction will not occur except by tunneling effects. The incident particle energy must be sufficient to overcome the Coulomb barrier and to overcome a negative Q of the reaction. Particles with energies below this barrier have a very low probability of reacting. The energy required to induce a nuclear reaction increases as the Z of the target material increases. For many low Z materials it is possible to use a low energy accelerator, but for high Z materials, it is necessary to increase the particle energy (Deconninick 1978).

The relation (Deconninick 1978) gives the number of reactions occurring in one second:

$$dn = I_0 N_A ds \sigma_{ab}$$

Where:

dn is the number of reaction occurring in one second

$I_0$  is the number of particles incident on the target in one second

$N_A$  is the number of target nuclei per gram

ds is the thickness of the material in grams per  $\text{cm}^2$

$\sigma_{ab}$  is the parameter called the cross-section expressed in units of  $\text{cm}^2$

In practical applications, the thickness ds of the material can be represented by a slab of thickness  $\Delta s$  thin enough that the cross-section can be considered as constant.  $N_A ds$  are

then the number of target atoms in a 1-cm<sup>2</sup> area of thickness  $\Delta s$ . If the target material is a compound rather than a pure element, then the number of nuclei per unit area is given by the expression:

$$N_A = \frac{F_A C \mathfrak{S}}{A_A}$$

Where:

- $N_A$  is the number of target nuclei per gram
- $F_A$  is the fractional isotopic abundance
- $C$  is the concentration in weight
- $\mathfrak{S}$  is Avogadro's Number
- $A_A$  is the atomic mass number of nucleus A

This leads to one of the basic facts of life in radioisotope production. It is not always possible to eliminate the radionuclidic impurities even with the highest isotopic enrichment and the widest energy selection. An example of this is given below in Figure 3 for the production of Iodine-123 with a minimum of I-124 impurity (Guillaume et al. 1975; Lambrecht and Wolf 1973; Clem and Lambrecht 1991; Qaim and Stöcklin 1983).

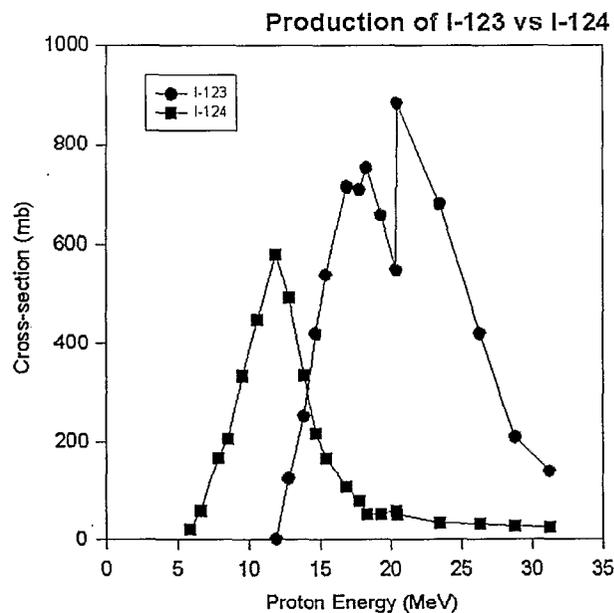


Figure 3. Plot of yield from the  $^{124}\text{Te}(p,n)^{124}\text{I}$  and the  $^{124}\text{Te}(p,2n)^{123}\text{I}$  nuclear reactions as a function of energy on target.

As can be seen from this graph, it is not possible to eliminate the I-124 impurity

completely during the I-123 production since the I-124 is being concurrently formed at the same energy. To minimize the I-124 impurity irradiation of the target at an energy where the production of I-124 is near a minimum becomes an option. In this case proton energy higher than 20 MeV will give a minimum of I-124 impurity.

#### Enriched Targets

Although generally supplementary in role to the applications in the production of radionuclides, stable isotopically labeled compounds find widespread uses in pharmacologic and toxicologic investigations. Their use as internal standards in such sensitive and specific analytical techniques as gas chromatography-mass spectroscopy and high pressure liquid chromatography coupled with mass spectroscopy is of great benefit in the assay of body fluids. The role of paramagnetic stable nuclides such as carbon-13 offers opportunities for nuclear magnetic resonance analyses of biological samples and possibly the whole body NMR in metabolic studies (Newman 1981; Meese et al. 1992; Browne and Szalio 1992).

Stable isotopes have for many years been the foundation for the production of radionuclides when radionuclidically pure isotopes are necessary. Since the invention of the "cyclotron" by Professor E.O. Lawrence in 1929 with proof of acceleration by M.S. Livingston in 1931, the accelerators have provided unique radionuclides for numerous applications.

In the past decade there has been a significant increase in the acquisition and use of "small" cyclotrons devoted principally to operation by chemists for the production of the biomedically useful radiolabeled compounds or radiopharmaceutical drugs. The primary impetus has been the acceptance of the potential for PET as a dynamic molecular imaging technique applicable to clinical diagnoses as well as providing the opportunity to evaluate novel radiotracers and radioligands for monitoring the "in vivo" biochemical or physiological processes at exquisite sensitivity.

Concurrent with the growth of PET/Cyclotron Facilities has been the emphasis on the production of increasing amounts of the short-lived, radionuclides in a chemical form for efficient synthetic application. Moreover, the radionuclidic purity of the final nuclide has been a concern. Targetry and target chemistry continue to be a factor in the synthetic chemist's consideration and appreciation of material science and radiation chemistry effects.

With energy constraints imposed by the various accelerators chosen for installation into imaging facilities, the availability and the application of stable enriched target materials for the production of the biologically equivalent radionuclides is of paramount concern. At this time the calutrons at Oak Ridge National Laboratory are no longer in service to prepare and to provide the numerous stable enriched nuclides needed for the variety of radionuclides being evaluated for clinical applications, moreover, concerns still plague many investigators who have experienced the lack or shortages in availability of such important target materials. A current example involves O-18 labelled water for F-18 production. The O-18 labelled water target is the choice of most centers

for the production of F-18 labeled fluoride anion utilized in the majority of fluorine-18 labeled radiopharmaceutical production (Finn and Johnson 1992; Finn 1999).

### Generator Produced Positron Emitting Radionuclides

The molybdenum/technetium-99m generator remains the dominant source for radionuclide availability in nuclear medicine departments when applied to radiopharmaceutical kit formulation. However, the impetus for change caused by the expanded application of PET radiopharmaceutical agents, including the equipment fusion of CT with PET or MRI with PET tomographs, will insure the continued growth and radiopharmaceutical development of short-lived, positron emitting diagnostic and potentially, therapeutic agents. In this regard, generator systems for specific PET radionuclides remain a potential resource in this developmental role.

Radionuclide generator systems consist of a parent radionuclide, usually a relatively long-lived nuclide which decays to a daughter nuclide, itself radioactive but with a shorter half-life. The system requires an efficient separation technique of the daughter nuclide from the parent. Conventionally, the parent is adsorbed onto a solid support and decays by particle emission. A solvent in which the daughter complex is soluble, is employed to elute (i.e. separate) the desired radionuclide. Unlike the Mo-99/Tc-99m generator developed at Brookhaven National Laboratory (Richards 1965a; Richards 1965b) which revolutionized the practice of nuclear medicine, the generator systems currently finding application to PET studies remain as primarily research sources for pharmaceutical development.

For those research centers and clinical facilities without the luxury of a cyclotron, several generator systems for production of positron emitting radionuclides have been proposed. Their production routes have been reviewed (Lambrecht 1983; Finn et al. 1983; Knapp and Butler 1984; Guillaume and Brihaye 1986; Qaim 1987; Welch and McCarthy 2000). Of the systems proposed, copper-62, gallium-68 and rubidium-82 radionuclides continue to find applications. The decay characteristics of these three generator systems are included in Table 1. A great deal of effort has been expended upon the production and construction of these generator systems, including investigations into solid support materials and elution characteristics.

The production routes for the parent radionuclide zinc-62 include the irradiation of a copper disc or copper-electroplated alloy to utilize the  $^{63}\text{Cu}(p,2n)^{62}\text{Zn}$  irradiation at optimal proton energy of 26-21 MeV (Robinson et al. 1980; Fujibayashi et al. 1989; Green et al. 1990; Zweit et al. 1992). The copper is dissolved in hydrochloric acid and the solution transferred to an anion-exchange resin column (AG 1X 8, 100-200 mesh, Cl<sup>-</sup> form). Copper is effectively eluted from the resin with 3 M HCl, and zinc-62 is eluted effectively with water. Following evaporation to dryness, the zinc is dissolved in 2 M HCl and adsorbed onto an anion-exchange column for periodic elution of the copper-62. Alternative routes to the preparation of the zinc-62 via irradiation of enriched nickel targets or zinc targets have been proposed, but have found only limited application

(Neirinckx 1977; Yagi and Kondo 1979; Piel et al. 1992).

Gallium-68 finds significant application in assessment of blood-brain barrier integrity as well as for tumor localization. It is widely used as a source for the attenuation correction of most positron emission tomographs. The parent germanium-68 is long-lived ( $t_{1/2} = 271$  d) and is generally not attempted on medium energy accelerators due to the low production yields (Pao et al. 1981; Loc'h et al. 1982). The primary source for the parent radionuclide is the spallation processes available at large energy accelerators where parasitic position and operation are available (Grant et al. 1982; Robertson et al. 1982). The recovery of the germanium-68 involves several multi-step chemical processes.

The earlier generator systems provided the gallium product in a complexed form as a result of either using solvent/solvent extraction techniques or chromatographic supports of alumina or antimony oxide. Refinements made to elute the gallium-68 in an ionic form were compromised by solubility problems of the oxide in the eluant and therefore slowed the potential for direct clinical use. Many of the limitations of previous chromatographic systems were overcome with the report of a tin oxide/HCl generator (Loc'h et al. 1980). The negative pressure generator consisted of tin oxide (0.16-0.25 mm diameter) contained in a glass column (10 mm diameter) between glass wool plugs atop sintered glass base. One normal HCl, with flow rate controlled by a valve at the base of the column serves as eluant. Results indicate a radiochemical yield approaching 80% in roughly 2 minutes time using 5 mL of eluant with the generator performance remaining high in spite of accumulated dose delivered to the solid support.

There are two types of chromatographic nuclide generator systems, i.e. positive or negative pressure. As is customary in all systems, the parent is adsorbed onto a column support commonly an organic exchanger or mineral exchanger which is contained within a borosilicate glass cylinder. The ends of the cylinder are terminated with a filter to insure minimal particular materials elution from the column and possibly for terminal sterilization by filtration in the case of the radionuclide used without further modification. As the half lives of the daughter nuclides become shorter, the opportunity for chemical manipulation prior to clinical administration is reduced to such an extent that the eluant must be physiologically acceptable, and quality assurance for parent breakthrough or exchanger breakdown becomes increasingly important. The column is housed within a lead or tungsten shield for radiation protection of the individuals utilizing the system. For efficient elution, attempts are made to both minimize the number of fittings and joints involved in preparing the system as well as to minimize the internal diameter and overall length of the cylindrical tubing.

Rubidium-82 is a myocardial blood flow agent and has found clinical application. The application of rubidium-82 chloride in diagnosis of ischemic heart disease and location of myocardial infarcts is an active area of application for this generator system (Gould 1988). The short half-life ( $t_{1/2} = 1.27$  m) of rubidium-82 and its similarity to potassium in biologic transport and distribution suggest that this generator-produced radionuclide might find a clinical role in thrombolytic therapy monitoring. The

myocardial uptake of Rb-82 is flow limited, being linear up to 2.5 times normal flow rates giving rise to underestimation and to overestimation of values (Goldstein et al. 1983; Selwyn et al. 1982). The production methods for the preparation of the parent radionuclide, strontium-82 have been studied quite extensively (Waters and Coursey 1987; Tarkanyi et al. 1988; Tarkanyi et al. 1990; Mausner et al. 1987). For this nuclide also, the spallation of molybdenum with high-energy protons is the production route of choice (Robertson et al. 1982; Thomas 1987).

The most commonly found generator system consists of an alumina column and uses 2% saline as eluent to achieve 85-95% elution efficiency. The generator system has a life span of approximately 3-4 months and requires periodic quality assurance for sterility, apyrogenicity, and measurement of breakthrough concentrations. The generator that is a positive pressure system operating pressures of 50-100 psi can function both in the bolus mode and constant infusion mode. In the latter case, the activity yield is a function of the flow rate (Yano et al. 1981).

**Table 1. Examples of Generators Yielding Positron Emitting Daughter Radionuclides of Clinical Interest**

Parent (Half Life)	Decay Mode (%)	Daughter (Half-Life)	Decay Mode (%)	Characteristic $\gamma$ -Energy(%)
Sr-82 (25 days)	EC(100)	Rb-82 (76 seconds)	$\beta^+$ (96),EC(4)	0.78 MeV (9)
Ge-68 (278 days)	EC(100)	Ga-68 (68 minutes)	$\beta^+$ (88),EC(12)	1.078(3.5)
Zn-62 (9.13 hours)	$\beta^+$ (18),EC(82)	Cu-62 (9.8 minutes)	$\beta^+$ (98)	1.17(0.5)
Xe-122 (20.1 hours)	EC(100)	I-122 (3.6 minutes)	$\beta^+$ (77),EC(23)	0.56(18.4)

#### Radionuclide generator equations

A synopsis of the equations to allow the calculation of the maximal concentrations of daughter nuclide from a particular generator, or the determination of the appropriate time to elute a generator is given through the following expressions (Finn et al. 1983).

Considering a simple radionuclide generator system of parent-daughter in which the half-life of the parent is longer than that of the daughter, the pair will eventually enter a state of transient equilibrium. This can be represented schematically as:



where A is the parent radionuclide which decays to the radioactive daughter B which in turn decays to the daughter nuclide C.

The ratio of decay of each radionuclide is described by the equation:

$$\frac{dN}{dt} = \lambda N \quad \text{or} \quad N = N_0 e^{-\lambda t}$$

Where N is the number of radioactive atoms at a specific time t and  $\lambda$  is the decay constant for the radionuclide and is equivalent to  $(\ln(2)/t_{1/2})$ .

Considering a generator system, the parent is generally adsorbed onto a solid support and serves as the sole source for the daughter radionuclide production. However, the number of daughter atoms present at any time t is described in a slightly more involved expression:

$$\frac{dN_B}{dt} = \lambda_A N_A - \lambda_B N_B$$

Since the daughter is decaying as well as being produced. The net rate of change on  $N_B$  with time is therefore indicated by the decay of A to B minus the decay of B to C. Substitution of the integral of the expression for A yields the net rate of change for B as:

$$\frac{dN_B}{dt} = \lambda_A N_A^0 e^{-\lambda_A t} - \lambda_B N_B$$

Integrating this equation to calculate the number of atoms of B at any time t gives:

$$N_B = \left( \frac{\lambda_A}{(\lambda_B - \lambda_A)} \right) N_A^0 (e^{-\lambda_A t} - e^{-\lambda_B t}) + N_B^0 e^{-\lambda_B t}$$

The first term on the right side of the equation represents the growth of the daughter nuclide B from the parent A decay and the loss of B through decay. The second term represents the decay of B atoms but since the parent A is generally considered a pure parent radionuclide upon generator manufacture, this term is zero. The equation can be rewritten in terms of activities and results in:

$$A_B = \left( \frac{\lambda_A}{(\lambda_B - \lambda_A)} \right) A_A^0 (e^{-\lambda_A t} - e^{-\lambda_B t})$$

Consideration of the general conditions for parent/daughter pairs, the cases are of transient equilibrium in which the parent half-life is greater than the daughter, or secular equilibrium in which the parent half-life is much greater than the daughter. Naturally if the decay should involve branching ratios, the equation must be appropriately modified.

Further, in the case of the PET generators, it is often useful to calculate the time when the daughter activity is at the maximum value,  $t_{\max}$ . Differentiation of the equation

with respect to time gives the result

$$t_{\max} = \ln \left( \frac{\left( \frac{\lambda_A}{\lambda_B} \right)}{(\lambda_B - \lambda_A)} \right)$$

The role of generators for the future of clinical PET remains uncertain at this time. The initial supposition that the generators hold potential for PET imaging at sites without a cyclotron or accelerator are being re-evaluated due to the costs associated with the procurement and scheduled availability of the parent radionuclide. Further, any supplementary equipment, such as that of the infusion system required for the strontium/rubidium generator, may result in low demand or choice of alternative radionuclides (Welch and McCarthy 2000).

### III. TARGETS AND IRRADIATION

#### Traditional PET radioisotopes

There are four positron-emitting radioisotopes that are considered the biologic tracers and their clinical and investigational uses are extensive. The radionuclides are fluorine-18, carbon-11, nitrogen-13 and oxygen-15. The reason these are so commonly used is that they can be easily substituted directly onto biomolecules. C-11, N-13 and O-15 are the “elements of life”. Substitution of carbon-11 for carbon-12 does not significantly alter the reaction time or mechanisms of a molecule. A similar situation exists for nitrogen-13 and oxygen-15. Fluorine-18 can often be substituted for a hydroxy group in a molecule or placed in a position where its presence does not significantly alter the biological behavior of the molecule. When the nucleus decays, the positron emitted will slow to thermal energies, annihilate upon interaction with an electron to produce two 511 keV gamma rays emitted at nearly 180° to each other. The decay characteristics of the positron emitting radionuclides allow the physiological processes occurring *in vivo* to be quantitated by detectors outside the body. Physiological modeling can be carried out using this information and quantitative assessments of the biological function can be made.

The positron emitting radionuclides are produced during the target irradiation and converted to a synthetic precursor, either in the target or immediately after exiting the target. The precursor is next converted into the molecule of interest. This chapter will only cover the targetry and the formation in the target of the chemical compound. The formation of precursors outside the target and the conversion of these precursors to the desired radiotracer will be covered in other chapters. The majority of the targets for the production of the biologic radionuclides have been either gases or liquids although there have been several solid targets developed.

The number and type of products, which are obtained in a target, are a function of

the irradiation conditions, the mixture of gases or liquids in the target and the presence of any impurities in the target or gas mixture. Changing the chemical composition or physical state of the target during irradiation (Firouzbakht et al. 1999) can alter the chemical form of the final product. These are all results of the “hot atom” chemistry and radiolysis occurring in the target during the irradiation. “Hot atom” is the term used to identify atoms with excessive thermal or kinetic energy, or electronic excitation. When an atom undergoes a nuclear transformation, it usually has a great deal of excess energy imparted from the incident bombarding particle and perhaps from the nuclear reaction. This energy can be manifested in any or all of the normal modes of excitation including rotational, translational or electronic. In nearly all cases the amount of energy present is sufficient to break all the existing chemical bonds to the atom and to send the newly transformed atom off with high kinetic energy. This energy is called the recoil energy and as the atom slows down, it imparts this energy to the surrounding environment. After the atom has transferred most of its excess energy to the surroundings and slowed to near thermal energies, it usually reacts chemically with the surroundings to form a compound. This compound may be stabilized or may undergo further reactions to form other chemical products.

Several distinguishing characteristics set these types of reactions apart from other chemical reactions. These are (Helus and Columbetti 1983): 1. The reactions are insensitive to the temperature of the surroundings, 2. They are independent of the phase of the reaction, 3. They are dependent on the radical scavengers present in the medium and 4. They are dependent on moderators in the medium such as inert gases. There have been several excellent reviews concerning the topic of hot atom chemistry (Wolf 1964; Welch and Wolf 1968; Ferrieri and Wolf 1983).

Another topic of importance in the preparation of radioisotopes is that of specific activity. It is important in several applications and particularly important in PET where the radionuclide is incorporated into a radiotracer that is used to probe some physiological process in which very small amounts of the biomolecule are being used. PET is basically a tracer method and the goal of the PET experiment is to probe the physiological process without perturbing that process. If the amount of radiotracer is very small in comparison to the amount of the native compound or its competitor, then the process will be perturbed very little. When carrying out such studies as probing the number of receptors or of the concentration of an enzyme, these considerations become even more important (Dannals et al. 1991).

The usual way to express the concept of specific activity is in terms of the amount of radioactivity per mole of compound. There is, of course, an ultimate limit, which occurs when there exists only the radioactive atoms or radiolabeled molecules. A table of the characteristics of the PET radionuclides presented in this chapter is given below (Fowler and Wolf 1982).

**Table 2: Decay characteristics for specific PET radionuclides.**

Nuclide	Half-life (min)	Decay Mode	Max. Energy	Mean Energy	Max. Range in water	Max. Specific Activity (theo.)
C-11	20.4	100% $\beta^+$	0.96 MeV	0.386 MeV	4.1 mm	9220 Ci/ $\mu$ mole
N-13	9.98	100% $\beta^+$	1.19 MeV	0.492 MeV	5.4 mm	18900 Ci/ $\mu$ mole
O-15	2.03	100% $\beta^+$	1.7 MeV	0.735 MeV	8.0 mm	91730 Ci/ $\mu$ mole
F-18	109.8	97% $\beta^+$	0.69 MeV	0.250 MeV	2.4 mm	1710 Ci/ $\mu$ mole
Cu-62	9.74	99.7% $\beta^+$	2.93 MeV	1.314 MeV	14.3 mm	19310 Ci/ $\mu$ mole
Ga-68	68.0	89% $\beta^+$	1.9 MeV	0.829 MeV	9.0 mm	2766 Ci/ $\mu$ mole
Br-75	96.0	75.5% $\beta^+$	1.74 MeV	0.750 MeV	8.2 mm	1960 Ci/ $\mu$ mole
Rb-82	1.25	95.5% $\beta^+$	3.36 MeV	1.5 MeV	16.5 mm	150400 Ci/ $\mu$ mole
I-122	3.62	75.8% $\beta^+$	3.12 MeV	1.4 MeV	15.3 mm	51950 Ci/ $\mu$ mole
I-124	6019.2	23.3% $\beta^+$	2.13 MeV	0.8 MeV	10.2 mm	31 Ci/ $\mu$ mole

As an example, typical specific activities for carbon-11 labeled molecules being reported are on the order of 10 Curies/ $\mu$ mole (370 GBq/ $\mu$ mole). Therefore it can be appreciated that only one in a thousand of the radiotracer molecules is actual labeled with carbon-11. The rest contain stable carbon-12. The specific activity is important in probing areas such as receptor binding, enzyme reaction, gene expression, and antigen binding with radiolabeled monoclonal antibodies.

In the area of monoclonal antibody labeling, there is the problem of the incorporation of the label into the molecule. If there is excessive carrier, then a smaller amount of the radiolabel will be incorporated into the molecule. This means that, in the case of a diagnostic radioisotope, it will more difficult to visualize or in the case of a therapeutic radioisotope, the dose to the target organ will be less than could be achieved. The specific activity of other PET tracers has been explored extensively. Some recent issues are the specific activity of radiotracers produced from the stable species (Link et al. 2000), bromine-76 (Forngren et al. 2000) and nitrogen-13 labeled ammonia (Suzuki et al. 2000a).

The radionuclide on which more effort has been expended in attempts to control specific activity has been carbon-11 and we will use that case as an example of the things that may be done in order to maximize the specific activity. Carbon-11 is a difficult case for achieving high specific activity because carbon is so ubiquitous in the environment. There can never be a truly carrier-free radiotracer labeled with carbon-11, but rather only one where no carrier carbon has been added and steps have been taken to minimize the amount of carbon which can enter the synthesis from outside sources. There can never be less carbon incorporated into the molecule than there is carbon present in the target

during the irradiation to produce the carbon-11. It is critical to use the highest possible purity of nitrogen gas in the target and to ensure that the target is absolutely as gas tight as it is possible to make it.

The walls of the target can also influence the specific activity since many alloys used to fabricate targets contain traces of carbon from the manufacturing process. During irradiation, these traces of carbon can make their way out of the target walls and into the gas phase where they will be incorporated into the final product. A correlation between the target surface area and the mass of carbon introduced into the synthesis has been observed and documented (Ferrieri et al. 1993; Suzuki et al. 2000b). Solvents used to clean the metal surfaces or oils left over from the fabrication process can also serve as sources for carbon in the targets. The input and output lines can also have the same or similar contaminants and such equipment as valves, connectors, insulators, regulators and flow controllers all can contribute to the carrier carbon and care must be taken to minimize the carbon added from these sources.

All the chemical reagents used in the synthesis may also add carrier carbon and need to be scrutinized in order to minimize this contribution.

### **Fluorine-18**

Fluorine-18 has a 109.8-minute half-life and decays 97% by positron emission. The other 3% is by electron capture. It forms very strong covalent bonds with carbon compounds and can be incorporated into a wide variety of organic molecules. It can be substituted for a hydroxy group as in the case of deoxyglucose or can be substituted for a hydrogen atom. The van der Waals radius of the fluorine atom is similar to that of the hydrogen atom and therefore substitution of fluorine for hydrogen causes very little steric alteration of the molecule. The concern with the fluorine for hydrogen substitution is that the electronegative nature of fluorine can alter the electron distribution in a way that will alter the binding properties of a molecule. In some ways however, fluorine is the most attractive of the four positron emitters commonly used in organic synthesis. The low energy of the positron gives the highest potential resolution in a PET camera. The range of the positrons with average energy in water is much less than 2 mm. The nearly two hour half-life allows for a more complex synthesis to be carried out within the decay time of the radioisotope. The electronic perturbation has also sometimes resulted in a molecule that has enhanced properties when compared to the original compound.

The most widely used radiotracer in PET by far is 2-[<sup>18</sup>F]fluoro-2-deoxyglucose (<sup>18</sup>FDG). It has proven to be of great utility in the measurement of the rate of metabolism in a wide variety of organs and disease states in humans.

### **Production Reactions**

There are a number of nuclear reactions, which can be used to produce fluorine-18. The major routes are the <sup>18</sup>O(p,n)<sup>18</sup>F reaction (Ruth and Wolf 1979) usually carried out on oxygen-18 enriched water or oxygen gas, and the <sup>20</sup>Ne(d,α)<sup>18</sup>F reaction (Casella et al. 1980). A number of other reactions are being used, but these two are the principal routes to fluorine-18.

The cross sections for these reactions have been explored extensively and the values are well characterized. The most common reaction is the proton reaction on enriched oxygen-18. The yield is significantly higher than the other reactions and the availability of low energy proton accelerators has made this the reaction of choice even in the face of the cost of the enriched oxygen-18 target material. The other common reaction, particularly for the production of electrophilic fluorine, is the  $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$  reaction on natural neon. The yield from this reaction is substantially less, but the ability to add other chemical constituents and the natural abundance target material are advantages (Guillaume et al. 1991; Helus et al. 1979; Helus et al. 1994).

### Targetry

The number and types of targets, which have been designed and fabricated for the production of fluorine-18, is very large. There have been several reviews of the types of targets (Guillaume et al. 1991; Blessing et al. 1986; Helus et al. 1979; Qaim 1989). For descriptive purposes, the targets can be divided into three basic categories. The first is the gas target primarily used for the production of electrophilic fluorine. The second is the liquid target, usually used for production of [ $^{18}\text{F}$ ]fluoride and the third are the solid targets, which are not commonly used for the production of fluorine-18.

For gaseous targets, there are two basic considerations. The first is the neon gas target. This target was used for many years for the production of [ $^{18}\text{F}$ ]F<sub>2</sub> from the  $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$  reaction (Casella et al. 1980, Guillaume et al. 1991). In this target, a small amount of fluorine gas, typically 0.1% to 0.2%, is added to the neon gas prior to irradiation. The design of the target has undergone significant changes from the first targets to the current design. The material of construction in the early targets was nickel or nickel alloys. The reason for this choice was that it was known that nickel parts would withstand a fluorine atmosphere and most fluorine handling systems were made from nickel or alloys such as Inconel or Monel which have a high nickel content. It was later shown that any surface, which could be passivated by fluorine, could be used in the fluorine target (Bishop et al. 1996). This discovery opened up the possibility of using aluminum target bodies for the production of elemental fluorine. The activation properties of aluminum are vastly superior to those of nickel or steel in terms of avoidance of the long-lived activities, which are produced within the target body during the bombardment. Target bodies constructed of aluminum significantly reduce the radiation dose received by the technical staff during the cleaning and maintenance of the target. A more extensive investigation of the properties of the surface has been made (Alvord et al. 1997; Helus et al. 1994). It was shown that aluminum, copper and nickel form fluoride layers and therefore passivate. The metal surfaces may also contain oxide layers as well. Only gold does not form a fluoride layer. Exposure to air after passivation does not alter the surface layer (Bishop 1996; Alvord et al. 1997).

The direct addition of fluorine to the neon before irradiation was one method for the recovery of the fluorine in elemental form. The other method was developed by Nickles (Nickles 1983) and is called the "two shoot" method. In this method the fluorine is allowed to stick to the walls of the target during the irradiations and is then removed by

creating a plasma containing elemental fluorine which reacts with the fluorine-18 on the walls and brings it into the gas phase. The usual gas for this target is the oxygen-18 enriched O<sub>2</sub> gas. Other methods for converting the fluorine-18 in other chemical forms such as HF to F<sub>2</sub> outside the target have also been attempted, but with limited success (Straatmann et al. 1982; Clark and Oberdorfer 1982). In this latter case, the neon or oxygen-18 enriched oxygen gas is irradiated and the fluorine allowed to stick to the walls. In some cases hydrogen is added to the target gas during irradiation. After irradiation, the target gas is removed and then the target is heated and flushed with hydrogen to bring the fluorine out in the form of HF (Blessing et al. 1986). The production of other fluorinating intermediates has also been described by using in-target chemistry, but these are not currently in widespread use (Lambrecht et al. 1978).

A high-energy reaction of protons on neon can also be used in the same way as the deuterons on neon (Lagunas-Solar and Carvacho 1995; Ruth 1985). The fluorine can be brought out of the target in the form of fluoride ion if the target is washed after irradiation with an aqueous solution (Blessing et al. 1986; Helus et al. 1979), or the glass liner of the target can be used directly as the reaction vessel (Nickles et al. 1983). In all cases, the fluorine is recovered from the surface in relatively high yields (>70%). Whether the protons on oxygen-18 or neon, or the deuterons on neon reaction is used, the result and the methodology is essentially the same.

By far the most commonly used target compound for the production of fluorine-18 in the form of fluoride ion is the oxygen-18 enriched water target. The basic design is relatively straightforward and similar in most of the targets being used routinely. There are wide variations, however, in the details of the design and of the materials of construction (Wieland et al. 1983; Kilbourn et al. 1984; Kilbourn et al. 1985; Keinonen et al. 1986; Berridge et al. 1986; Iwata et al. 1987; Mulholland et al. 1989; Huzar et al. 1985; Vogt et al. 1986; O'Neil et al. 1997; Gonzales-Lepera et al. 1997; Steel et al. 1997; Roberts et al. 1995). The primary constraint is to use as little of the oxygen-18 enriched water as possible while leaving enough volume to take maximum advantage of the cross-section and to absorb or transfer the heat created by the passage of the beam. A typical target is shown in Figure 4.

There are several considerations in the operation of the target. The first is the fact that the water is boiling unless the pressure in the target is increased to diminish or inhibit the boiling (Heselius et al. 1989; Pavan et al. 1997; Steinbach et al. 1990). To decrease this problem, the target may be run under elevated pressure of helium, nitrogen or some other inert gas, or the target may be valved off and allowed to find its own pressure level. In this case, pressure can exceed 40 atmospheres especially if the water has not been completely degassed prior to use. Since there is a relatively thin foil containing the pressure, there is a limit to the beam current that can be applied in this situation.

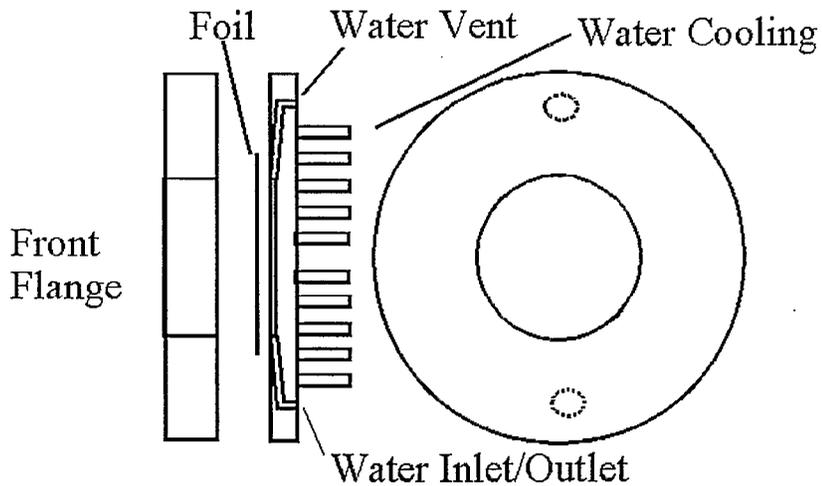


Figure 4. Typical water target for the production of fluorine-18 from oxygen-18 enriched water

The decision to operate at low or high pressure will also impact on the target fabrication and the materials chosen for the target. The radiolysis products of the water will have different effects depending on the conditions inside the target. The material of construction of the target can also have an effect on the chemical reactivity of the fluoride obtained from the target (Schlyer et al. 1993; Solin et al. 1988; Zeisler et al. 1997). If the target is operated at low pressure, there will be some loss of the water out of the beam strike area due to bubble formation (Berridge et al. 1986; Heselius et al. 1989).

There have been some unique target designs for the water target using spherical targets (Becker and Erbe 1997) or flowing targets (Iwata et al. 1987) or frozen oxygen-18 enriched carbon dioxide targets (Firouzbakht et al. 1993). The helium-3 or alpha reaction on natural water has also been used to produce fluorine-18 for synthesis (Nozaki et al. 1974; Fitschen et al. 1977; Qaim and Stöcklin 1983). These targets work in exactly the same way as the proton on water targets with the exception of the higher level of heat deposition with the heavier particles. The targets are not commonly used because of the substantially lower yields.

### Radioisotope Separation

There are two separate cases for recovery of the fluorine-18 from the target. In the case of the gas target, the fluorine (with the carrier  $F_2$ ) is removed from the target as a gas mixture and can be used in the synthesis from there. In the case of the water target, the activity is removed in the aqueous phase. There are two general methods after that. The first is to use the oxygen-18 water containing [ $^{18}F$ ]fluoride ion directly in the synthesis. This method is used by several investigators who have small volume water targets and the cost of losing the oxygen-18 water is minor compared to the cost of the cyclotron irradiation. The other method is to separate the fluoride from the oxygen-18 water either by distillation or by using a resin column (Schlyer et al. 1990; Mock et al. 1996; Pascali et al. 1997). When the resin is used, it also separates the metal ion impurities from the enriched fluoride solution that, in general, increases the reactivity of the fluoride.

### Carbon-11

Carbon-11 has a 20.4 minute half-life and decays 99.8% by positron emission and only 0.2% by electron capture. It decays to stable boron-11. Carbon-11 offers the greatest potential for the synthesis of radiotracers which track specific processes in the body. The short half-life limits processes that can be studied. The chemical form of the carbon-11 can vary depending on the environment during irradiation. The usual chemical forms of carbon-11 obtained directly from the target are carbon dioxide and methane.

### Production Reactions

There are several reactions used to produce carbon-11. By far the most common reaction is the  $^{14}\text{N}(p,\alpha)^{11}\text{C}$  reaction on nitrogen gas (Bida et al. 1980; Casella et al. 1978). This reaction gives a high yield of carbon-11 and with the addition of trace amounts of oxygen, gives the carbon-11 almost exclusively in the chemical form of carbon dioxide.

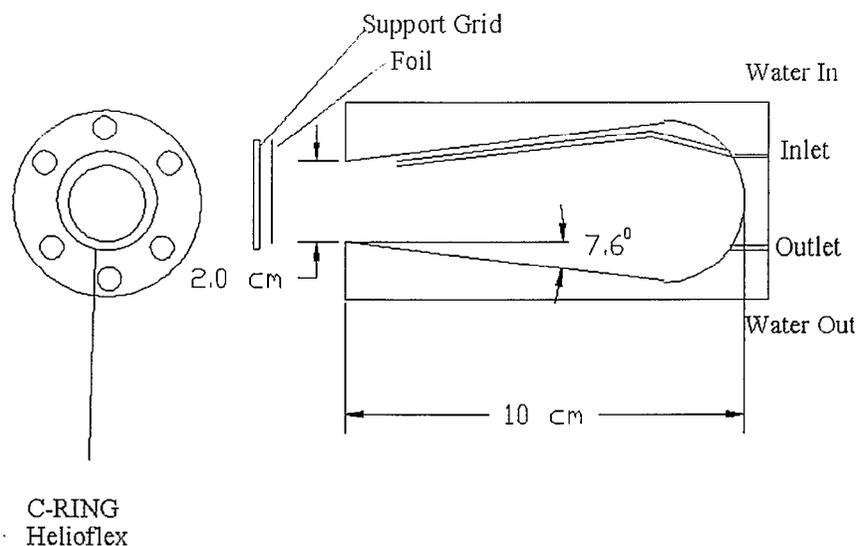


Figure 5. Typical gas target for the production of radioisotopes from gaseous targets

### Targetry

Carbon-11 targets can be either gases or solids. The basic design of the gas target has not changed a great deal since the first targets were developed (Christman et al. 1975; Clark and Buckingham 1975). The basic body design is an aluminum cylinder, which can be held at high enough pressure to stop the beam or at least degrade the energy below the threshold of the reaction being used. A typical gas target is shown in Figure 5.

The choice of aluminum for the target body is a result of the excellent activation properties. The activation products are produced in relatively small amounts or have a short half-life. This aids in the maintenance of the target since the radiation dose to the technician is greatly reduced. The usual labeled product from the gas target is carbon dioxide (Christman et al. 1975; Ferrieri and Wolf 1983; Finn et al. 1971; Helus et al. 1986) and methane, but other products have been attempted (Finn et al. 1971; Helus et al. 1986; Buckley et al. 2000).

Some recent advances in the design of gaseous targets for the production of carbon-11 are the realization that carrier carbon was being added by the surface of the aluminum (Ferrieri et al. 1993), that the target was more efficient if it was conical taking into consideration the fact that the beam was undergoing multiple scattering through the foil window and in the gas (Schlyer and Plascjak 1991; Helmeke and Hundeshagen

1995). and that the density of the gas was significantly reduced at high beam currents (Wieland et al. 1984; Heselius et al. 1982; Heselius et al. 1987).

The foil material used on these targets is also important in several respects. If the beam energy is high enough, then a relatively thick aluminum foil may be used to contain the gas. If the beam energy is lower, then a thinner foil must be used and aluminum does not have sufficient tensile strength to withstand the pressures that are built up inside the target during irradiation. In this case a thin foil of Havar or other high tensile strength material can be used to withstand the pressures. It is also possible to place grids across the foils in order to increase the burst pressure of the foils (Hughey et al. 1991; Schlyer and Firouzbakht 1996).

Some solid targets have been used for the production of carbon-11. These are, for the most part, boron-oxide either enriched or natural abundance. A typical target for this would be a stepped plate similar to the inclined plane target used for a variety of isotopes. The difference is that here the powder is pressed into the grooves of the target plate and irradiated (Clark and Buckingham 1975). The difficulty of removing the carbon from the matrix in comparison to the ease of separation in the gas target has made the solid target less widely used.

#### Radioisotope Separation

The separation of carbon-11 in the gas target is a simple matter since the carbon-11 is usually in the form of carbon dioxide when it comes out of the target. The nitrogen gas used as the target material is usually inert in chemical reactions and therefore the target gas can be passed through a solution for reaction. The carbon dioxide can also be removed by trapping either in a cold trap or on an adsorbent substrate such as molecular sieves. From there the carbon-11 can be used to produce a wide variety of precursors.

The separation of the carbon dioxide from the solid matrix of the boron oxide is a more difficult problem, but can be accomplished under the correct conditions. The target containing the boron oxide is contained in a gas tight box (Clark and Buckingham 1975). A sweep gas is passed through the box during irradiation. The beam heating is sufficient to cause the boron oxide to melt and the carbon dioxide is released into the sweep gas. The labeled gas is trapped down stream and the irradiation is continued until sufficient carbon-11 has been collected for use in the synthesis. The advantage of this type of target is that, once made, it can be used repeatedly without further maintenance.

#### Nitrogen-13

Nitrogen-13 decays by pure positron emission (100%) to stable carbon-13. As with carbon-11, the short half-life somewhat restricts the potential utility of this radionuclide. Several compounds incorporating nitrogen-13 have been made, but the time of accumulation in the body is short and so the physiological processes which may be studied must be rapid (Straatmann and Welch 1973; Tilbury and Emran 1991). By far the most widely used compound of nitrogen-13 for PET is in the chemical form of ammonia. It is used as a blood flow tracer and has found utility in cardiac studies to determine areas of ischemic or infarcted tissue.

## Production Reactions

There are several reactions leading to the production of nitrogen-13. The reactions which are commonly used are the  $^{13}\text{C}(p,n)^{13}\text{N}$  reaction (Firouzbakht et al. 1991; Austin et al. 1975), the  $^{12}\text{C}(d,n)^{13}\text{N}$  reaction (Firouzbakht et al. 1991) and the  $^{16}\text{O}(p,\alpha)^{13}\text{N}$  reaction (Sajjad et al. 1986; Parks et al. 1978).

The proton on carbon-13 reaction has an advantage in that it requires a low incident proton energy, but suffers from the disadvantage of requiring isotopically enriched material. The most common reaction is the  $^{16}\text{O}(p,\alpha)^{13}\text{N}$  reaction on natural water (Tilbury and Dahl 1979; Tilbury et al. 1977; Helmeke et al. 1997; Mulholland et al. 1990).

## Targetry

The target for the production of nitrogen-13 can be either solids, liquids, or gases depending on the chemical form of the nitrogen that is desired. The chemical form can also be changed by a number of other factors such as the dose and dose rate to the target, the pH of the liquid targets and the physical state.

The first target for the production of N-13 was a solid target of boron that was bombarded by an alpha beam by Joliot and Curie (Joliot and Curie 1934). Solid targets have been used for the production of nitrogen-13 particularly in the form of either nitrogen gas or in the form of ammonia (Shefer et al. 1994; Ferrieri et al. 1983; Dence et al. 1994). Solids mixed with liquids have also been used particularly in the production of ammonia (Bida et al. 1986; Alvord et al. 1997; Zippi et al. 1995). Solid targets of frozen water have also been used to produce ammonia (Firouzbakht et al. 1999).

Liquid targets are by far the most popular and widely used. The reaction of protons on natural water produces nitrate and nitrite ions, which can be converted to ammonia by reduction (Tilbury et al. 1977; Tilbury and Dahl 1979; Tilbury and Emran 1991; Wieland et al. 1995; Helmeke et al. 1997). The water target can also be used to form ammonia directly with the addition of a reducing agent or with a radical inhibitor (Berridge and Landmeier 1993; Korsakov et al. 1996; Medema et al. 1997; Mulholland et al. 1990; Wieland et al. 1991; Bida and Satyamurthy 1995). The chemistry involved in the production of the final product distribution in the water target has been a topic of interest and debate (Tilbury and Dahl 1979; Patt et al. 1991; Sasaki et al. 2000; Firouzbakht et al. 1999) and it has been found that high dose irradiation of the physical form of water results in the formation of oxidized species while the same irradiation of ice maintains the initial distribution of reduced products (Firouzbakht et al. 1999).

Gas targets have also been used particularly in the production of nitrogen gas, but there have also been attempts to use the gas target for the production of ammonia (Mikecz et al. 1997; Welch et al. 1968; Straatmann et al. 1977).

## Radioisotope Separation

The separation of the nitrogen-13 from the solid target is usually accomplished by

burning or heating the solids (McCarthy et al. 1997; Ferrieri et al. 1983; Dence et al. 1994). The water target with no additives usually produces nitrogen-13 in the chemical form of nitrates and nitrites. The conversion of the nitrogen, nitrates or nitrites to other chemical forms will be discussed elsewhere.

### Oxygen-15

Oxygen-15 is the longest lived of the positron emitting isotopes of oxygen. The half-life is 122 seconds and it decays by 99.9% positron emission. It decays to stable nitrogen-15. It was one of the first artificial radioisotopes produced with low energy deuterons on a cyclotron (Livingston and McMillian 1934). Oxygen-15 is used to label gases for inhalation such as oxygen, carbon dioxide and carbon monoxide, and it is used to label water for injection. The major purpose of these gases and liquids is to measure the blood flow, blood volume and oxygen consumption in the body.

### Production Reactions

There are several reactions for the production of oxygen-15. The most common are the  $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$  reaction (Del Fiore et al. 1979; Retz\_Schmidt et al. 1960; Vera-Ruiz and Wolf 1977), the  $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$  reaction (Sajjad et al. 1984) and the  $^{16}\text{O}(\text{p},\text{pn})^{15}\text{O}$  reaction (Beaver et al. 1976). Of these reactions, the ones that are use commonly are the deuterons on natural nitrogen gas, the protons on enriched nitrogen-15 nitrogen gas and the protons on natural oxygen when specific activity is not an issue as in the case of oxygen gas or labelled water.

### Targetry

The targets for these compounds are, for the most part, gaseous targets. The oxygen-15 containing compound can be made either directly in the target (Vera-Ruiz and Wolf 1978; Votaw et al. 1986; Harper and Wickland 1981) or outside the target in a separate recovery module. The gas targets are usually nitrogen gas bombarded with either protons or deuterons dependent upon the accelerator characteristics.

Solid targets have been explored as a source for producing [ $^{15}\text{O}$ ]ozone (Wieland et al. 1997). In this target, irradiating quartz micro-fibers and allowing the nucleogenic atoms that exit the fibers to react with the surrounding gas produces the oxygen-15.

### Radioisotope Separation

The radioisotopes can be separated or, in some circumstances, the target gas can be used with a minimum of processing (Strijckmans et al. 1985; Wieland et al. 1986; Beaver et al. 1976). An example of this is the production of [ $^{15}\text{O}$ ]water. It can be made directly in the target by adding 5% hydrogen to the nitrogen gas in the target (Vera-Ruiz and Wolf 1978). In this case the water is produced directly. Ammonia is concurrently produced in the target as a radiolytic product of the nitrogen and hydrogen and it must be removed. The other option is to produce oxygen-15 labeled oxygen gas in the target and then process it to water outside the target. Details of these procedures can be found elsewhere. The water has also been produced by bombarding water using the  $^{16}\text{O}(\text{p},\text{pn})^{15}\text{O}$  reaction with a final clean up on an ion exchange column (Van Naemen et al. 1996).

## Novel Solid Targets for PET Radiopharmaceutical Preparation

The most well known medical application of cyclotrons is the production of radionuclides for diagnostic studies applied to nuclear medicine and the nuclear sciences. Yields of most of the medically used radionuclides produced with cyclotrons utilizing a variety of nuclear reactions and energies have been reported (Pagani et al. 1997; Qaim 1989; Chaudhir 1979; Qaim 1982).

The increasing amount of clinically relevant data available from PET studies involving the biologic tracers has contributed to the expanding interest in additional positron emitting radionuclides in order to investigate both basic research studies and additional clinical applications. The spectrum of physiologic processes that could potentially be studied grows as the number of "alternative" positron emitting radionuclides (Pagani et al. 1997) that can be prepared increases. With the introduction of the new generation of cyclotrons that are capable of delivering hundreds of microamperes of beam current, the potential for increased amounts of numerous radionuclides can no longer be considered as limited by the beam fluence, but rather by the optimal thermal performance of the particular target materials and target backings. This is particularly true in the case of the cooling-water/target backing interface and beam profile considerations for solid target stations now becoming available on some of the nominal "baby" cyclotrons.

Iodine-124, a radionuclide, which has potential for both diagnostic and therapeutic applications, is an important example. This nuclide was often viewed as an unwanted radionuclidic impurity in the production of iodine-123 from the energetic proton irradiation of tellurium targets at cyclotron facilities engaged in the commercial production of iodine-123. Iodine-124 has a half-life of 4.18 days and decays by positron emission (23.3%) and electron capture (76.7%). Although several nuclear reactions have been suggested for its production, the precise measurement of the excitation function for the  $^{124}\text{Te}(p,n)^{124}\text{I}$  reaction (Qaim et al., 1999; Scholten et al. 1995) indicates its suitability for use on low energy cyclotrons. A detailed preparation of this radionuclide via the  $^{124}\text{Te}(p,n)^{124}\text{I}$  nuclear reaction on low energy cyclotrons has recently been published which uses a reusable target composed of windowless aluminum oxide and enriched tellurium-124 oxide solid solution matrix. The radioiodide is effectively recovered using a dry distillation process with the volatile iodine species being trapped on a thin Pyrex glass tube coated with a minute amount of sodium hydroxide. Recovery of the radioiodine from the tube was nearly quantitative however, the recovery of the radioiodines from the target was somewhat less (65-75%) and appears to be a function of the crystal structure of the tellurium oxide that was irradiated (Sheh et al. 2000).

Another element within the halogen family that possesses several radioisotopes of potential clinical use is bromine. In particular, bromine-75 ( $t_{1/2} = 1.6$  h,  $I_{\beta+} = 75.5\%$ ,  $E_{\beta+} = 1.74$  MeV) has several nuclear reactions reported for its production but only the proton

irradiation processes appear suitable for medium energy cyclotrons (>25 MeV) (i.e.  $^{76}\text{Se}(p,2n)^{75}\text{Br}$ ). The major impurity associated with the proton process is bromine-76. The optimal production conditions for the proton irradiation of enriched selenium-76 targets utilized an incident energy of 30 MeV degraded within the target to 22 MeV and had a reported production rate of Br-75 of 100 mCi/uAh with an impurity level for the Br-76 reported at 0.9% (Qaim 1986). Several selenides such as those of silver or copper have been found as suitable targets for irradiation at low beam currents (Paans et al. 1980; Vaalburg et al. 1985) and an external rotating target system was reported for preparation of radiobromine from the low melting elemental selenium target (Kovacs et al. 1985). Losses of selenium-76 were noted at approximately 1% after a one hour irradiation period at 20 uA for this target system.

As in the case of radioiodine, the separation of the radiobromine from the selenium-76 irradiated target material was effected by thermochromographic evolution at 300 C followed by dissolution of the bromine in a small volume of hot water. The radiochemical yield for the overall process was not exceedingly high, and this as well as the difficulties associated with targetry using highly enriched selenium nuclides may be part of the reason that the application of this procedure for the preparation of bromine-75 is not more widely employed.

The more widely used method for the production of bromine-75 requires the acceleration of helium-3 particles of energies nominally 36 MeV onto arsenic target materials (Blessing and Qaim 1984; Blessing et al. 1982).

## V. CONCLUSION

Nuclear Medicine is the specialty of medical imaging, which utilizes a variety of radionuclides incorporated into specific compounds for diagnostic imaging and therapeutic applications. During recent years, research efforts associated with this discipline have concentrated on the decay characteristics of particular radionuclides and the design of unique radiolabeled tracers necessary to achieve time-dependent molecular images. The specialty is expanding with specific PET and SPECT radiopharmaceuticals allowing for an extension from functional process imaging in tissue to pathologic processes and nuclide directed treatments. PET is an example of a technique that has been shown to yield the physiologic information necessary for clinical oncology diagnoses based upon altered tissue metabolism.

Most PET drugs are currently produced using a cyclotron at locations that are in close proximity to the hospital or academic center at which the radiopharmaceutical will be administered. In November 1997, a law was enacted called the Food and Drug Administration Modernization Act of 1997 which directed the Food and Drug Administration (FDA) to establish appropriate procedures for the approval of PET drugs in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act and to establish current good manufacturing practice requirements for such drugs. At this time the FDA is considering adopting special approval procedures and cGMP requirements for

PET drugs. The evolution of PET radiopharmaceuticals has introduced a new class of "drugs" requiring production facilities and product formulations that must be closely aligned with the scheduled clinical utilization. The production of the radionuclide in the appropriate synthetic form is but one critical component in the manufacture of the finished radiopharmaceutical.

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