

# Cyclotron Produced Radionuclides: Operation and Maintenance of Gas and Liquid Targets



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CYCLOTRON PRODUCED  
RADIONUCLIDES:  
OPERATION AND MAINTENANCE OF  
GAS AND LIQUID TARGETS

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CYCLOTRON PRODUCED  
RADIONUCLIDES:  
OPERATION AND MAINTENANCE OF  
GAS AND LIQUID TARGETS

INTERNATIONAL ATOMIC ENERGY AGENCY  
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## FOREWORD

The application of radionuclides in medicine has undergone significant growth in the past decade, and one of the major factors contributing to this increased growth is the availability of a large number of cyclotrons exclusively dedicated to this purpose. In an IAEA survey in 2006, it was estimated that there are more than 700 cyclotrons available in Member States. Many of these cyclotrons are dedicated to the production of positron emission tomography isotopes, more specifically,  $^{18}\text{F}$  for the production of [ $^{18}\text{F}$ ]FDG (2- [ $^{18}\text{F}$ ]-fluoro-2-deoxy-D-glucose). Many of these cyclotrons use liquid targets for the production of  $^{18}\text{F}$  and gas targets for the production of  $^{11}\text{C}$ .

The IAEA had, in the past, initiated several projects to support radionuclide production using cyclotrons and, in response to Member State needs in building up the expertise in the field, decided to compile a technical publication covering the production of radionuclides using gas and liquid targets of current and potential interest, as a companion to the existing guidelines on the use of solid targets (Standardized High Current Solid Targets for Cyclotron Production of Diagnostic and Therapeutic Radionuclides, Technical Reports Series No. 432 (2004)).

Work towards the preparation of the current publication was initiated during a consultants meeting held in Vienna in February 2009. In line with the recommendation of the consultants meeting, the book incorporates relevant information regarding radionuclide production in gas and liquid targets, with a special emphasis on the production of radionuclides of general interest to the nuclear medicine community. This IAEA publication was compiled using inputs from dedicated experts in the field, as well as the results of the coordinated research project Improved High Current Liquid and Gas Targets for Cyclotron Produced Radioisotopes, completed in 2010. Consequently, this book contains chapters on the technology behind targetry, techniques for the preparation of targets, irradiation of targets under high beam currents, target processing, target recovery, etc. This publication is intended to be a resource for scientists interested in translating this technology into practice; technologists already working in Member States with cyclotrons who want to enhance the utility of the existing machines; and managers who are in the process of setting up facilities in their countries. In addition, students working towards higher level degrees in related fields may also benefit from the information in this book.

The IAEA wishes to thank all of the contributors to this publication, especially D. Schlyer for compiling and reviewing the book. The IAEA officer responsible for this publication was M. Haji-Saeid of the Division of Physical and Chemical Sciences.

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# 1. INTRODUCTION

Radionuclides produced with a cyclotron, and their corresponding radiopharmaceuticals, are extremely valuable in basic medical research, disease diagnosis and radiotherapy treatment. There are more than 700 cyclotron facilities worldwide for the purpose of producing radionuclides for clinical use, and the number is growing every year. The overall goal of this publication is to provide some practical advice on using gas or liquid targets for the production of the most widely used radionuclides. Almost everyone's goal in the production of these radionuclides is to use targets that are reliable and produce higher specific activities. The issue of solid targets for radioisotope production ( $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{103}\text{Pd}$ ,  $^{210}\text{Tl}$ ) has been addressed in Technical Reports Series No. 432 [1.1].

Until recently, cyclotrons, and the related targetry, were mainly operated by a rather small group of specialist scientists and engineers, situated either within academic physics research institutions or large university hospitals, or with the few industrial scale radionuclide manufacturers. However, because of the rapidly spreading use of positron emission tomography (PET) and PET/CT (computed tomography), the number of cyclotron installations is expanding rapidly, and target technology needs to be understood by a much larger group of scientists. Although many of the new cyclotron installations are primarily erected for the production of a single isotope ( $^{18}\text{F}$ ) in the form of a single, well defined radiopharmaceutical, [ $^{18}\text{F}$ ]FDG (2- $^{18}\text{F}$ ]-fluoro-2-deoxy-D-glucose), a sizeable fraction of all these new groups has declared and started active research programmes looking at  $^{11}\text{C}$  compounds, other  $^{18}\text{F}$  compounds, and the use of non-traditional positron emitting radiotracers such as  $^{64}\text{Cu}$  and  $^{68}\text{Ga}$ .

For the most commonly used PET radiopharmaceutical, [ $^{18}\text{F}$ ]FDG, specific activity (SA) is not a problem, but there is a clear need for reliable production of other pharmaceuticals with high specific radioactivity. Present day tracers, and certainly future tracers, include receptor/transporter ligands that, in order to be true tracers, need to keep the receptor occupancy with the radiolabelled tracer below 1%; this is necessary to avoid pharmacological or pharmacodynamic effects.

High SA for the typical  $^{11}\text{C}$  and  $^{18}\text{F}$  products and labelling intermediates creates a challenge for various radioanalytical techniques. Methods used are typically chromatographic and include gas chromatography (GC) and high pressure liquid chromatography (HPLC).

Despite the routine manufacture of large amounts of  $^{18}\text{F}$  fluoride for FDG production and other positron emitting radiotracers, expert skills in targetry, and a good understanding of the interplay between the cyclotron, the target and subsequent labelling chemistry are not presently widely available but are essential to continued deployment and development. A similar situation holds for

gas targets producing the clinically important single photon emission computed tomography (SPECT) radioisotopes,  $^{123}\text{I}$  and the  $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$  generator.

## 1.1. QUESTIONS RAISED FOR GAS AND LIQUID TARGETS

During the experts' meetings that led to this publication, several important questions were raised and discussed. These include:

- Which targets are currently important to the user community?
- Which targets will be important in the near future?
- Which targets are currently underdeveloped and need further research to achieve their potential?
- How can new targets be developed to withstand higher beam current and, therefore, utilize the full capabilities of modern cyclotrons?
- What research can be done to improve performance in targets?
- How can novel methods of producing the product or precursor 'on-line', such as the use of 'in-target' chemistry, be improved to produce the desired product?
- How can the recovery/recycle chemistries of enriched target materials be refined?
- How can it be ensured that recycled materials will meet production standards?
- How can methods be developed for quality control of the pre-irradiation target?
- How can target diagnostics be used during irradiation?
- How can beam entry windows for gas targets be improved? What material properties are the most important?
- How can current research be extended to make it most useful to the radionuclide production community?

These questions are explored in this publication. The experience that has been gained over the years can answer some of these questions, but a great many still need answers.

## 1.2. TARGETS EXAMINED

The cyclotron targets investigated in this book are:

- $^{18}\text{O}$  water: for production of  $^{18}\text{F}$  with protons;
- $^{14}\text{N}$  gas: for production of  $^{11}\text{C}$  with protons;

- $^{16}\text{O}$  liquid: for production of  $^{13}\text{N}$  with protons;
- $^{15}\text{N}$  gas: for production of  $^{15}\text{O}$  with protons;
- $^{14}\text{N}$  gas: for production of  $^{15}\text{O}$  with deuterons;
- $^{20}\text{Ne}$  gas: for production of  $^{18}\text{F}_2$  with deuterons;
- $^{18}\text{O}$  gas: for production of  $^{18}\text{F}_2$  with protons;
- $^{124}\text{Xe}$  gas: for production of  $^{123}\text{I}$  with protons;
- $^{82}\text{Kr}$  gas: for production of  $^{81}\text{Rb}$  with protons.

The targets examined were chosen because they are the most widely used targets. Fluorine-18 is by far the most widely used cyclotron produced radionuclide, and, therefore, the water target using  $^{18}\text{O}$  enriched water is one of the targets chosen for detailed examination. Since the same target can be used to produce  $^{13}\text{N}$  by replacing the enriched water with natural water, the characteristics that apply to one also apply to the other. The second target chosen was  $^{14}\text{N}$  for  $^{11}\text{C}$  production. There are a couple of reasons to choose this target, but SA is one of the great challenges for this target because  $^{12}\text{C}$  is everywhere in our environment. Achieving high SA with this target will result in methods for eliminating a carrier for all gas targets. The same target can again be used to produce  $^{15}\text{O}$ , by substituting  $^{15}\text{N}$ , enriched nitrogen gas, for the natural nitrogen gas used in the  $^{14}\text{N}$  target.

To produce  $^{18}\text{F}$  labelled fluorine gas for electrophilic reactions, there are two potential targets that can be used. These are the ( $^{18}\text{O}$ ) enriched oxygen gas target and the neon target. These targets share some characteristics and problems. They also have differences, but these are mainly in the methods used to extract the fluorine from the target after irradiation.

The last two are the xenon target for the production of  $^{123}\text{I}$  and the ( $^{82}\text{Kr}$ ) krypton gas target for the production of  $^{81}\text{Rb}$ . Again, these two targets have a great deal in common. They both use inert gases as the target material, and both use similar methods to extract the final product from the target.

The lessons learned in examining these targets can be applied easily to other types of gas and liquid targets. The physical characteristics of the construction materials will be the same, and the problems of heat transfer, chemical inertness and impurity of radionuclides will be similar.

The unedited report of the coordinated research project Improved High Current Liquid and Gas Targets for Cyclotron Produced Radioisotopes, as presented at the final research coordination meeting, provides additional supporting material and case studies [1.2].

## REFERENCES TO SECTION 1

- [1.1] INTERNATIONAL ATOMIC ENERGY AGENCY, Standardized High Current Solid Targets for Cyclotron Produced of Diagnostic and Therapeutic Radionuclides, Technical Reports Series No. 432, IAEA, Vienna (2005).
- [1.2] INTERNATIONAL ATOMIC ENERGY AGENCY, Improved High-current Liquid and Gas Targets for Cyclotron Produced Radioisotopes (Proc. Research Coordination Mtg Vienna, 2009), IAEA, Vienna (2009).

## 2. COMMON TARGET MATERIALS AND PRODUCTION CONSIDERATIONS

Gas and liquid targets almost always consist of a solid target body containing the fluid and a thin foil that encloses the target material and yet allows penetration of the beam. This foil may be supported by a grid to increase the pressure that the foil can withstand. The physical and chemical characteristics of these two target components can have significant effects on:

- Temperatures inside the target;
- The chemical form of the radionuclide;
- Radionuclide impurities that may find their way into the final product;
- Maintenance frequency;
- The useful life of the target.

In this chapter, the characteristics of the target body with supported or unsupported foils, and how the foils' qualities influence the target attributes will be discussed. Further information on the theory of target design can be found in the IAEA publication *Cyclotron Produced Radionuclides: Principles and Practice* [2.1].

### 2.1. TARGET BODY MATERIALS

Several common materials are used for fabrication of target bodies. The ideal materials should be strong, able to withstand high pressures, be chemically inert under gas plasma conditions, and have a good thermal conductivity. Six target body materials constitute 99% of the gas and liquid target bodies in routine use. These are aluminium, titanium, nickel, niobium, tantalum and silver. The properties of each of these metals are described in the following sections, followed by a summary of the physical characteristics in Section 2.1.7.

#### 2.1.1. Aluminium

The more commonly used alloy of aluminium, which is used in the fabrication of target bodies, is aluminium 6061-T6. The composition of the alloy is given in Table 2.1.

TABLE 2.1. COMPOSITION OF ALUMINIUM 6061-T6

Component	Weight (%)
Al	95.8–98.6
Cr	0.04–0.35
Cu	0.15–0.40
Fe	≤0.70
Mg	0.8–1.2
Mn	Maximum 0.15
Other, each	Maximum 0.05
Other, total	Maximum 0.15
Si	0.4–0.8
Ti	Maximum 0.15
Zn	Maximum 0.25

#### 2.1.1.1. *Material notes*

In general, aluminium 6061 combines relatively high strength, good workability and high resistance to corrosion. It has excellent joining characteristics and is widely available. The 6061-T8 and 6061-T9 alloys offer better chipping characteristics over the 6061-T6 alloy, but for target fabrication the T6 type is the most common. Other uses include aircraft fittings, camera lens mounts, couplings, marine fittings and hardware, electrical fittings and connectors, decorative hardware, hinge pins, magneto parts, brake pistons, hydraulic pistons, appliance fittings, valves and valve parts, and bike frames. Aluminium reacts with air to grow its own thin oxide coating very rapidly. This hard, dark grey coating protects the metal.

#### 2.1.1.2. *Cleaning*

Normally, aluminium needs no cleaning when used as a target body. If it becomes discoloured or corroded, it can be cleaned with mild abrasive and water. Targets used for the production of high SA <sup>11</sup>C should not be exposed to organic solvents except under unusual circumstances. In such a case, the surface must be rinsed with distilled water several times and then dried with dry nitrogen before use.

### 2.1.2. Titanium

Titanium has several advantageous characteristics. It is lightweight, strong and corrosion resistant. The alloys have good tensile strengths ranging from 210–1380 MPa (30 000 to 200 000 psi) similar to those found in some steel alloys. Titanium has a corrosion resistance similar to that of platinum, but with a density that is only 56% of that of steel.

There are many alloys of titanium that can be used in the construction of cyclotron targets. However, commercially pure, grade 1 titanium is the most commonly used. The composition and characteristics of some of these alloys are given in Table 2.2.

TABLE 2.2. COMPOSITION AND CHARACTERISTICS OF TITANIUM ALLOYS

Alloy	Standard	Density (g/cm <sup>3</sup> )	Melt range (°C ± 15)
Commercially pure	ASTM grade 1	4.51	1670
Commercially pure	ASTM grade 2	4.51	1677
Commercially pure	ASTM grade 3	4.51	1677
Commercially pure	ASTM grade 4	4.54	1660
Ti–3%Al–2.5%V	ASTM grade 9	4.48	1704
Ti–0.8%Ni–0.3%Mo	ASTM grade 12	4.51	—
Ti–3%Al–8%V–6%Cr–4%Zr–4%Mo	Beta C	4.81	1649
Ti–15%Mo–3%Nb–3%Al–0.2%Si	Timetal 21 S	4.90	—
Ti–6%Al–4%V	ASTM grade 5	4.42	1649
Ti–2.5%Cu	IMI 230	4.56	—
Ti–4%Al–4%Mo–2%Sn–0.5%Si	IMI 550	4.60	—
Ti–6%Al–6%V–2%Sn		4.54	1704
Ti–10%V–2%Fe–3%Al		4.65	1649
Ti–15%V–3%Cr–3%Sn–3%Al		4.76	1524
Ti–8%Al–1%Mo–1%V		4.37	1538
Ti–11%Sn–5%Zr–2.5%Al–1%Mo	IMI 679	4.84	—
Ti–5.5%Al–3.5%Sn–3%Zr–1%Nb–0.3%Mo–0.3%Si	IMI 829	4.54	—
Ti–5.8%Al–4%Sn–3.5%Zr–0.7%Nb–0.5%Mo–0.3%Si	IMI 834	4.55	—
Ti–6%Al–2%Sn–4%Zr–2%Mo		4.54	1649
Ti–6%Al–2%Sn–4%Zr–6%Mo		4.65	1635
Ti–6%Al–5%Zr–0.5%Mo–0.2%Si	IMI 685	4.45	—
Ti–6%Al–3%Sn–4%Zr–0.5%Mo–0.5%Si	Ti 1100	4.50	—

### *2.1.2.1. Cleaning*

Titanium can be cleaned effectively with nitric acid alone or in combination with hydrochloric acid. Nitric acid alone is also an excellent way to passivate the titanium surface. Acid cleaning of titanium surfaces to remove deposits is sometimes necessary. Acid cleaning cycles can be used provided proper inhibitors are present. Ferric ion, as  $\text{FeCl}_3$ , is very effective as an inhibitor for titanium in acid solutions. For instance, as little as 0.1% (by weight)  $\text{FeCl}_3$  will inhibit corrosion of titanium by hydrochloric acid. At ambient temperatures, a solution of 25% (by weight) of HCl can be safely used on titanium, with  $\text{FeCl}_3$  used as an inhibitor.

### **2.1.3. Nickel**

Nickel is a relatively hard, malleable and ductile metal which is a fairly good conductor of heat and electricity. The surface of nickel can be passivated with nitric acid, but it will dissolve in other weak acids. There are many alloys of nickel with a wide variety of different properties. One of the most widely used is stainless steel. There are some target bodies made of stainless steel in use. Target bodies made of other nickel alloys are common, particularly with corrosive gases such as the halogens. For example, monel is an alloy of nickel and copper (e.g. 70% nickel, 30% copper, with traces of other elements) that has good resistance to corrosion by dilute fluorine gas.

### *2.1.3.1. Cleaning*

Nickel targets can be washed with a mild detergent in warm water and rinsed thoroughly and air dried. For stubborn stains, one can make a paste of baking soda and water or alcohol, cover the item with the paste and allow the paste to dry, run under warm water and buff dry with a mild abrasive pad. Commercial silver cleaning polish can be used on silver and nickel, if the baking soda paste does not remove the tarnish.

### **2.1.4. Niobium**

Niobium is a component of some stainless steels and also alloys with non-ferrous metals. These alloys have good strength and other properties. The metal has a low capture cross-section for thermal neutrons and so finds use in some applications in the nuclear industry and in cyclotron targetry. It is very inert at room temperatures, but has poor chemical resistance at elevated temperatures and can easily be attacked by oxygen, halogens and even carbon. Due to this

reactivity at higher temperatures, machining of niobium is best carried out in a protective atmosphere such as argon. This also makes niobium a good choice for low temperature targets (such as water), but perhaps not the best choice for higher temperature gas targets.

#### *2.1.4.1. Cleaning*

To properly clean niobium, the following steps are recommended:

- Degrease;
- Immerse in commercial alkaline cleanser for 5–10 min;
- Rinse with water;
- Immerse in 35–40% HNO<sub>3</sub> for 2–5 min at room temperature;
- Rinse with tap water and follow by a rinse with distilled water;
- Force air dry.

### **2.1.5. Tantalum**

Tantalum is one of the refractory metals that offers a valuable combination of properties. It can be handled easily at room temperature. Its strength at elevated temperature is low compared with tungsten and molybdenum. Tantalum's corrosion resistance is unusually good in most commercial combinations of acids. It has several unique properties that have made it essential to certain applications, making it well worth the high cost. It offers approximately the same corrosion resistance to most acids and caustics as glass. In addition, it can be fabricated by bending, roll forming and welding with relative ease, by personnel experienced with the metal. Tantalum's ductility and density have made it popular with the military for armour penetration. Its density and nuclear stability make it a valuable material for containers of radioactive elements.

#### *2.1.5.1. Cleaning*

Tantalum can be cleaned with steel grit in a bead blaster and then rinsed with hot hydrochloric acid to remove traces of iron from the steel beads. The tantalum surface is inert to hydrochloric acid even at elevated temperatures. Tantalum surfaces can be cleaned with hot chromic acid solution (a saturated solution of potassium chromate in hot concentrated sulphuric acid). After this treatment, the tantalum surface should be very thoroughly rinsed with distilled water to remove any traces of the cleaning solution.

## 2.1.6. Silver

Silver metal has several very useful characteristics for the construction of targets. It has the highest thermal and electrical conductivity of all the metals although cold working the silver will reduce the conductivity. It is quite easily machined, being only a little harder than gold. It does not react with air, water or many acids under normal conditions. It does tarnish with exposure to very active oxidizing species such as ozone. This reaction can be seen in water targets after high current irradiations.

### 2.1.6.1. Cleaning

Washing soda ( $\text{Na}_2\text{CO}_3$ ) can be used to clean large pieces of silver. For targets, one can combine the soda with ethyl or isopropyl alcohol to form a paste, dip a clean, damp sponge into the paste and rub it onto the silver, then scrub with cotton swabs until something approaching a mirror finish is restored to the silver, and finish by rinsing the silver with hot distilled water in an ultrasonic bath, followed by drying; the longer the paste is left on the silver, the more tarnish will be removed. If the silver is being used for cleaning a water target for the production of  $^{18}\text{F}$ , toothpaste, which is a common method for cleaning, should be avoided because the fluoride that is commonly in the toothpaste will greatly decrease the SA of the  $^{18}\text{F}$ .

## 2.1.7. Materials summary

A summary of the important physical characteristics of the above target body metals is presented in Table 2.3.

TABLE 2.3. TARGET BODY PROPERTIES

Property	Aluminium	Titanium	Nickel	Niobium	Tantalum	Silver
Thermal conductivity ( $\text{W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ )	167	21.9	90.9	53.7	57	429
Melting point ( $^{\circ}\text{C}$ )	582	1725	1453	2410	3290	961
Chemical inertness	Fair	Good	Fair	Excellent	Excellent	Good
Heat capacity ( $\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ )	24.2	24.9	26.1	24.6	25.3	25.4

## 2.2. TARGET WINDOW MATERIALS

The materials used for target windows need to be very strong in thin sheets and maintain their strength at elevated temperatures. The materials used most frequently for target windows are Havar, aluminium, niobium and titanium. The last three are also used as target bodies, and, therefore, most of the characteristics are listed in the previous section. One important characteristic that is critical to foils is the yield strength as a function of temperature.

### 2.2.1. Havar

Havar is a cobalt base alloy that has a wide variety of useful properties, the most useful of which in cyclotron targetry is the very high strength at high temperatures. Havar will retain 75% of its strength at room temperature up to 510°C. This property is particularly useful for target foils and Havar is quite widely used in this application. The endurance lifetime can be maximized by heat treating the alloy at 540°C after 80% cold work.

Typical analysis of Havar shows: Co (42%), Cr (19.5%), Ni (12.7%), W (2.7%), Mo (2.2%), Mn (1.6%), C (0.2%), Fe balance.

### 2.2.2. Materials summary

A summary of the important characteristics for foil materials is given in Table 2.4.

Target windows always have a heat load, owing to the energy the beam deposits in passing through them. This heat can be dissipated in different ways, depending on the choice of foil material and the thickness. Aluminium has a

TABLE 2.4. TARGET FOIL CHARACTERISTICS

Property	Aluminium	Titanium	Havar	Niobium
Thermal conductivity ( $\text{W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ )	167	16.4	14.7	53.7
Melting point (°C)	582	1725	1480	2410
Density ( $\text{g}/\text{cm}^3$ )	2.71	4.5	8.3	8.6
$dE/dx$ ( $\text{keV}/\mu\text{m}$ ) for 10 MeV protons	9.2	13.5	24.2	21.2
Tensile strength (25°C), psi (MPa)	42 000 (290)	63 000 (434)	270 000 (1860)	85 000 (585)

rather low melting point, but can get rid of heat through conduction (high thermal conductivity). Heat emission removal mechanisms cannot be used, since aluminium melts before radiation becomes a significant mechanism. Havar, on the other hand, loses most of its heat by convection and radiation and very little through conduction, owing to the very low thermal conductivity and the fact that it maintains its strength at high temperatures. Titanium and niobium lie somewhere in between these two extremes and, depending on thickness and size, can dissipate heat by any of the three methods.

A primary consideration is the strength of the foil as it heats up. The yield strength versus temperature for these four materials is presented in Fig. 2.1. The superiority of Havar in yield strength is clear, as is the fact that it can withstand fairly high temperatures without significant loss in yield strength.

### 2.3. GRIDS — ADVANTAGES AND DISADVANTAGES

One way to increase the pressure a target foil can withstand is to support the foil with a grid. This is especially important with low energy accelerators, where a thinner foil means a higher energy on the target and, therefore, a better production yield. There are several designs for grids, including circular holes and

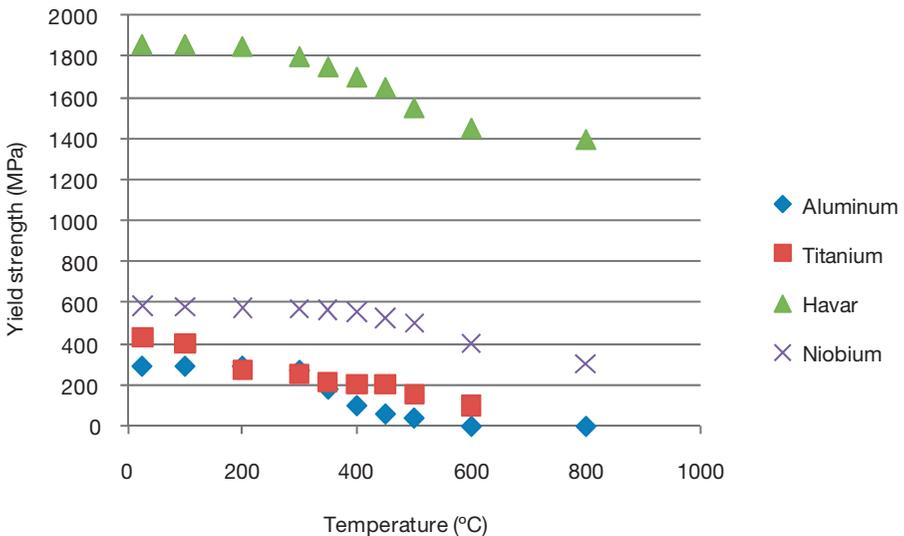


FIG. 2.1. Yield strength versus temperature for a series of metals commonly used as foils for cyclotron targets.

hexagonal arrays. The grids with circular holes are limited to about 78% transmission, while grids with a hexagonal design have a much higher transmission. There are several reasons to boost the operating pressure of gas and liquid in cyclotron targets:

- To achieve thick gas target conditions while minimizing the contaminating effects of wall surfaces;
- To raise the boiling point of liquids to assist heat transfer;
- To drive the end products over long distances through narrow bore ‘tuned pipelines’.

The pressure that the foil will withstand can be fairly accurately predicted using some simple calculations [2.2]. Plane stress predicts rupture at a pressure  $p_o = 2St/R$  for a foil thickness  $t$ , tensile strength  $S$ , covering a circular aperture and deforming with radius  $R$ . The rupture limit suggests a choice of foil materials with high tensile strength at the operating temperature, and a small aperture radius. The latter can be accomplished by supporting the foil with a multihole grid [2.3–2.5]. This further provides a high conductivity pathway for the ‘thermal grounding’ of the foil through the grid septa. The limit of grid transparency increases from 78% for parallel rows of circular holes to about 86% for a close packed array of hexagonal holes. These more complicated patterns usually require electric discharge machining (EDM). Foil activation ( $^{65}\text{Cu}(p,n)^{65}\text{Zn}$ ) studies performed with and without the intervening grid show that an optical transparency of 86% is reduced to about 80% in practice for a typical non-paraxial beam, owing to the fact that the beam is not uniform over the area of the foil grid. If necessary, the measured beam emittance can be incorporated into the EDM grid fabrication. This refinement would match the grid’s optical acceptance to the beam divergence, and would further reduce the heat load on the grid, while only modestly increasing the EDM complexity. This refinement would require a careful measurement of the beam divergence, employing any of several types of beam profile monitor spaced along the beam axis. This measurement can be rather simply made by copper foil activation, with the resulting  $^{65}\text{Zn}$  activity imaged by GafChrome film or phosphor plates. An even simpler technique is to pass the beam through an isolation foil, allowing the beam to enter the room to impinge on a thick block of dry ice (solid  $\text{CO}_2$ ). Within a few seconds at an incidence of a few microamps, a conical hole that outlines the beam profile along the beam axis will be vaporized through the block. This outline can be captured by filling the hole with water, or molten wax, to measure the divergence needed for aligning the septa of the EDM-formed grid.

In practice, a paraxial hexagonal grid of aluminium (0.25 mm septa, 3 mm across the flats, 6 mm axial depth) supporting a 25  $\mu\text{m}$  Havar foil can operate at pressures up to 100 bar (100 MPa) covering a 1 cm beam strike. The EDM process employs a tungsten rod as the etching electrode, and its diameter determines the ‘break’, or radius, which results at the corners of each hexagonal hole. A 0.010 in (0.25 mm) ‘break’ has proven to be excellent for stress relief at high operating pressures.

A singular case arises where the gridded single foil alternative proves to be inferior to the He-cooled double window, namely in the case where extremely corrosive gases are irradiated. An example of such a case is the ‘two-shoot’ technique to produce gaseous  $^{18}\text{F}_2$  for electrophilic fluorination. In this case, a first irradiation of pure  $^{18}\text{O}_2$  produces the  $^{18}\text{F}$ , which is trapped on the target walls, allowing quantitative cryo-recovery of the enriched oxygen gas. Then, a second irradiation of a dilute solution of fluorine in an inert gas such as krypton [2.6] is performed. During this bombardment, which is needed to exchange  $^{18}\text{F}$  adsorbed on the target walls with the gaseous carrier fluorine, a single gridded Havar foil may fail and result in pinhole formation within seconds. In this case, the double foil approach with forced He cooling resolves the issue.

In summary, the advantages of the gridded single foil approach include:

- Simplicity, in the absence of a He recirculating system;
- Higher operating pressures to assist in heat transfer;
- Shortened gas target dimensions to reduce contaminants;
- Slightly higher beam energy on target, at the cost of about 20% beam current loss on the grid.

The helium cooled double foil technique has the advantages of a conventional approach, suitable for even corrosive target materials. Attempts to exploit tandem targets by using nitrogen as the coolant gas, stripping out  $^{11}\text{CO}_2$  for small scale developmental chemistry, have proved to be ineffective, adding needless complexity and poor SA.

Another disadvantage of the gridded approach occurs when the grid is relatively thick. As an example, in one experiment, a slight misalignment in the beam direction resulted in a loss of production. When the beam was at  $90^\circ$  to the grid, 945 mCi (34.97 GBq) of  $^{11}\text{C}$  was obtained, but when the incident beam was at a slight angle, the production yield went essentially to zero, since the beam was stopped in the thick front grid. Care must be taken to ensure that the beam is aligned with the grid or a loss in production greater than the transmission loss will occur.

## 2.4. POTENTIAL RADIONUCLIDES PRODUCED IN FOILS AND TARGET BODIES

When these foils are bombarded with charged particles, some impurity radionuclides may be produced. These have the potential to make their way into the final product unless care is taken to ensure that they are removed. A list of these potential radionuclides is given in Table 2.5.

Havar presents a special case since it has so many components in the alloy. There are a number of radionuclides produced during irradiation. Table 2.6 shows a list of the major radionuclide impurities produced in Havar foils.

TABLE 2.5. POTENTIAL RADIONUCLIDES PRODUCED IN FOILS AND TARGET BODIES

Target	Particle	Reaction products
$^{27}\text{Al}$	p, d, $\alpha$	$^{22,24}\text{Na}$
$^{\text{nat}}\text{Ti}$	p, d, $^3\text{He}$ , $\alpha$	$^{48,49,51}\text{Cr}$ , $^{48}\text{V}$ , $^{43,44\text{m},44\text{g},47,48}\text{Sc}$
$^{\text{nat}}\text{Ni}$	p, d, $^3\text{He}$ , $\alpha$	$^{62,63,65}\text{Zn}$ , $^{60,61,64,67}\text{Cu}$ , $^{56,57}\text{Ni}$ , $^{55,56,57,58,60,61}\text{Co}$ , $^{52,54,56}\text{Mn}$ , $^{48}\text{V}$
Havar	p	See Table 2.6
$^{93}\text{Nb}$	p, d, $\alpha$	$^{94\text{g},95\text{m},95\text{g},96\text{mg}}\text{Tc}$ , $^{90,93\text{m}}\text{Mo}$ , $^{89,90,91\text{m},92\text{m},95\text{mg}}\text{Nb}$ , $^{86,87,88,89}\text{Zr}$ , $^{86,87\text{m},87,88}\text{Y}$
$^{\text{nat}}\text{Ag}$	p, d, $\alpha$	$^{108\text{g},108\text{m},109\text{mg},110\text{g},110\text{m},111\text{mg},112\text{m}}\text{In}$ , $^{107,109}\text{Cd}$ , $^{105,106\text{m},110\text{m}}\text{Ag}$ , $^{100,101,103}\text{Pd}$ , $^{99,100,101\text{m},102,105}\text{Rh}$ , $^{97}\text{Ru}$

TABLE 2.6. RADIONUCLIDE IMPURITIES PRODUCED IN HAVAR FOILS

Product	$T_{1/2}^{\text{a}}$	Reaction	Threshold (MeV)
$^{55}\text{Co}$	17.5 h	$^{58}\text{Ni}(p,\alpha)$	1.36
$^{56}\text{Co}$	77 d	$^{56}\text{Fe}(p,n)$	5.44
$^{57}\text{Co}$	272 d	$^{57}\text{Fe}(p,n)$	1.65
		$^{60}\text{Ni}(p,\alpha)$	0.27
		$^{58}\text{Ni}(p,2p)$	8.31
$^{58}\text{Co}$	71 d	$^{58}\text{Fe}(p,n)$	3.14
$^{57}\text{Ni}$	35.6 h	$^{58}\text{Ni}(p,pn)$	12.43
$^{51}\text{Cr}$	27.7 d	$^{52}\text{Cr}(p,pn)$	12.27
$^{52}\text{Mn}$	5.6 d	$^{52}\text{Cr}(p,n)$	5.60
$^{95}\text{Tc}$	20 h	$^{95}\text{Mo}(p,n)$	2.50
$^{96}\text{Tc}$	4.3 d	$^{96}\text{Mo}(p,n)$	3.80
$^{181}\text{Re}$	19.9 h	$^{182}\text{W}(p,2n)$	10.65
$^{93\text{m}}\text{Mo}$	6.85 h	$^{93}\text{Nb}(p,n)$	3.60

<sup>a</sup>  $T_{1/2}$  = half-life.

#### **2.4.1. Practical yields for production of some common radionuclides in liquid and gas targets**

The rate of production and the typical yields are the important parameters for radionuclide production. Table 2.7 gives some yield data for the list of radionuclides produced in liquid and gas targets [2.7–2.21].

### **2.5. DIAGNOSTIC TOOLS**

The routinely used, commercial cyclotrons have few diagnostic tools to offer in terms of monitoring target performance during cyclotron runs. Typically, only the beam current on target and the target pressure are read out. Even the total activity at the end of bombardment (EOB) is most often missed, as the target activity is normally loaded directly into the synthesis modules under remote control, and, thus, an important parameter is missed. The EOB out-of-target activity could serve to discriminate between important shortcomings either on the cyclotron/target side or in the synthesis itself.

There are other parameters that could be useful as diagnostic tools. For example, on gridded targets, the beam current on the grid versus that on the target could determine whether the beam is incident at the optimum angle. The SA of the CO<sub>2</sub> for a carbon target could be used to see whether impurities are somehow getting into the target, which would be indicative of a small leak developing. The rate of flow of cooling water is important to ensure adequate cooling on the target. The front foil temperature could be monitored by infrared, to ensure that the foil is not getting too hot, which in turn could result in a ruptured foil.

Monitoring of these parameters must usually be done with custom equipment, since most cyclotron manufacturers do not offer such monitoring as standard equipment.

#### **2.5.1. Beam profile measurements**

It is well known that cyclotrons have variable beam profiles, depending on a number of parameters, such as the condition of the ion source, the beam intensity, the main magnetic field, the thickness and condition of the stripper foil, etc. A minimum requirement is that the beam profile should match the aperture of the target, but it should preferably fulfil additional requirements. Hot spots will be detrimental to the window foils, and can add to the ‘channelling’ of the high intensity beam through gas or liquid targets. It has also been proposed that the beam profile in the gas, and perhaps in the liquid targets, can influence the internal circulation patterns and the chemical fate of the radioactive species formed.

TABLE 2.7. PRODUCTION PARAMETERS OF PET ISOTOPES FROM LIQUID AND GAS TARGETS

Isotope	Target	Reaction	Energy range (MeV)	Saturation yield (GBq/ $\mu$ A)	Practical yield	Remark		
$^{18}\text{F}$	$^{18}\text{O}$ water or gas	(p,n)	18–2.5	13.8	90 GBq (30 $\mu$ A, 75 min)	Water		
					56 GBq (30 $\mu$ A, 90 min)	Water		
					8.1 GBq/ $\mu$ A	Water		
	$^{20}\text{Ne}$ gas	(d, $\alpha$ )	20–1.5	4.67	2 GBq/ $\mu$ A	Gas		
1 GBq/ $\mu$ Ah (16.5 MeV)					Gas			
1.07 GBq/ $\mu$ Ah (10.5 MeV)					Gas			
40–120 MBq (6.5 MeV)					Gas			
$^{11}\text{C}$	$^{14}\text{N}$ gas	(p, $\alpha$ )	18–4	8.7	192 GBq (30 $\mu$ A, 60 min, 22 MeV)	Gas		
					11–4	3.32	2.96 GBq/ $\mu$ A	Gas
					$^{16}\text{O}$ liquid	(p, $\alpha$ )	18–6	1.74
11–6	0.58	0.25 GBq/ $\mu$ A	Liquid					
8–6	0.16	0.12 GBq/ $\mu$ A	Liquid					
$^{15}\text{O}$	$^{14}\text{N}$ gas	(d,n)	14.2–0	5.14	4.2 GBq/ $\mu$ A (12.3 MeV)	At saturation		
					11–0	3.94	3.6 GBq/ $\mu$ A (10.7 MeV)	At saturation
					8–0	2.59	2.5 GBq/ $\mu$ A (8.28 MeV)	At saturation
	$^{15}\text{N}$ gas	(p,n)	18–4	7.06	5.7 GBq/ $\mu$ A (16 MeV)	At saturation		
					11–4	2.06	2.6 GBq/ $\mu$ A (11 MeV)	At saturation
					8–4	1.71	1.6 GBq/ $\mu$ A (11 MeV)	At saturation
$^{123}\text{I}$	$^{124}\text{Xe}$ gas	(p,x)	13–2	31.1	>370 kBq/ $\mu$ Ah	Gas		
					54 MBq/ $\mu$ Ah (31.1 MeV)	Gas		
					>90 MBq/ $\mu$ Ah	Gas		
					350 MBq/ $\mu$ Ah (30 to >12 MeV, 120 $\mu$ A)	1100 KPa Gas		
$^{81}\text{Rb}$	$^{82}\text{Kr}$ gas	(p,2n)	29.3–0	3.015	1.6 MBq/ $\mu$ Ah	Gas		
					18–0	0.344	0.296 MBq/ $\mu$ Ah	Gas

Many research groups at the larger cyclotron centres have implemented various beam viewers and beam scanners. These devices are, however, very often current limited and/or are interceptive, blocking the beam while measuring.

If the beam profile (the relative beam distribution over the admittance area of the target) for a given cyclotron was known to be independent of beam intensity, existing diagnostic tools (beam viewers and scanners) could be inserted before and at intervals during production at low to medium intensities (1–5  $\mu\text{A}$ ), to establish the position and profile, then withdrawn from the beam and only the intensity increased (by increasing the ion source output).

For routine use at smaller production cyclotrons with no or a limited beam line, a simple beam profiling tool in the form of a glowing wire mesh is an alternative. This system is a passive, static device consisting of an open mesh of a refractory metal placed permanently in the beam under thermally isolated conditions. The parts of the mesh that are struck by the beam will heat up. If the mesh wires are sufficiently thin, the heat will only be dissipated by radiation, meaning that the wires will glow proportionally to the local power density of the part of the beam intercepted. To some approximation, the heat emitted will follow the Stefan–Boltzmann law that the radiated power is proportional to the fourth power of the temperature ( $T^4$ ). This requires that transverse heat conduction along the mesh wires is much smaller than the heat lost by radiation.

To the extent that the mesh grid size is smaller than any local spatial variation in the beam, the radiated light deconvoluted by the  $T^4$  function will give the local power density in the beam. Meshes of tantalum, rhenium and tungsten have been tested. All materials give about equal light output and all have tolerated beams up to 10  $\mu\text{A}$ . Beams of over 20  $\mu\text{A}$  have been tolerated for several minutes; however, the light output in these conditions overexposed the charge coupled device (CCD) camera used.

The mesh can be positioned at an angle of  $45^\circ$  to the external proton beam of the cyclotron. One side of a normal beam line can be equipped with a clear glass window, through which a simple CCD based web camera is directed and focused on the mesh. The opposing blind flange carries the foil supported (and electrically grounded) by thin stainless steels screws (Fig. 2.2).

A conventional water cooled four-sector collimator in front of the mesh, and a water cooled dummy target immediately downstream from the mesh, collect the entire beam transmitted through the mesh. The mesh and dummy target can be mutually isolated to give the total intensity distribution (intercepted and transmitted).

With thinner wires on the same mesh size, higher transmission and less light output could probably be found. In addition, thinner wires will have lower thermal conductance, favouring heat transfer by radiation. (The thermal



FIG. 2.2. Fine wire mesh used to determine the beam profile.

conductance scales with the square of wire diameter, while heat emission by radiation scales with the surface of the wire and is proportional to the first power of wire diameter.) At the same time, however, the power deposited in the wire decreases more or less linearly with wire diameter, as long as the wires are much thinner than the stopping range of the beam in the mesh material.

As an example, the range of 16 MeV protons in tantalum is about  $740 \text{ mg/cm}^2$ , corresponding to 0.46 mm. This meets the requirement of a ‘thin’ wire in the stopping range of the beam.

Under these conditions, the wire diameter loses its importance for wire temperature, and the wire thickness can be minimized to optimize transmission. However, the mesh should still be self-supporting.

### 2.5.2. Choice of mesh material

Table 2.8 compares the melting point and thermal conductivity of the three preferred materials.

TABLE 2.8. PROPERTIES OF MESH MATERIALS

Element	Melting point (°C)	Thermal conductivity ( $\text{W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ )
Tantalum	3017	57
Rhenium	3186	48
Tungsten	3422	170

From these data, rhenium should be preferred as having the highest melting point and the lowest thermal conductivity. However, the difference between tantalum and rhenium is not of great importance.

Although this method has been used in practice, there are still considerations for the long term use of this system:

- The survival time of the metal mesh inside the beam line vacuum is not known.
- Optical systems and/or cameras need to be less sensitive to radiation damage than a CCD camera. Resistance to neutron damage is particularly important.
- The light versus temperature curve needs to be calibrated for the given camera system.
- The mathematical deconvolution of the beam power distribution from the temperature data could be investigated, taking wire thermal conductance into consideration.

One of the important parameters that needs to be monitored during irradiation is the fraction of the beam that is actually producing radionuclides. This can be lower than expected, owing to effects such as density reduction and misdirection of the beam into the collimator or walls of the target.

### **2.5.3. Beam profile scanner**

A commercial beam profile monitor with a 50 mm scanning aperture can be installed in a beam line of the cyclotron, if there is a beam line. The scanner has a helical tungsten wire rotating through the beam, first in the horizontal direction and, subsequently, in the vertical direction. The tungsten wire itself is electrically grounded, and the signal is picked up as secondary electrons by a cylindrical collector electrode wrapped around the scanning wire movement envelope. Holes of 50 mm diameter are available for entrance and exit of the beam, which never hits the collector itself. The readout of the current on the collector electrode is done on an oscilloscope, using a trigger derived from the rotation of the scanning wire.

## **2.6. IN-BEAM SPECTROSCOPY**

In-beam spectroscopy of prompt neutrons and gamma rays is the standard tool of nuclear physics to study nuclear reactions and structure. Over the past century, the techniques have advanced from the Curies' alpha induced reactions,

to accelerators to modern measurements resolving fine structure in excitation energy as a function of angle and polarization. It is somewhat ironic that the most relevant literature for the PET radiochemist comes from early work (1950s to 1960s). At that time, cross-section data were compiled that summed over angles and final states, and unabashedly listed excitation functions for  $X(a,b)Y$  that are exactly the information that is needed today to predict the practical yields of the radionuclides that enter the PET chemistry chain.

The instruments employed in the detection of prompt gamma rays and neutrons during irradiation advanced over the years to achieve ever higher resolution (energy, time, polarization, etc.), as demonstrated by:

- Gamma rays: Geiger–Müller tubes; NaI + photomultipliers; high resolution Ge-detectors;
- Neutrons:  $\text{BF}_3$ ; long counters; organic scintillators with  $n$ - $\gamma$  discrimination; time-of-flight techniques.

These instrumental advances called for specific laboratory conditions: spacious vaults and well collimated detectors to reduce wall effects, distant targets, robust detectors insensitive to neutron activation, and, most importantly, sensitivity matched to the event rate at low beam currents. Each of these criteria is directly at odds with the typical PET production site, where a 10–20 MeV cyclotron is shoe-horned into a tight, shielded bunker, with thick targets crowded close to the accelerator receiving 100  $\mu\text{A}$  beams. Since the thick-target saturation production rate for  $^{18}\text{O}(p,n)^{18}\text{F}$  is of the order of 200 mCi (7400 MBq)/ $\mu\text{A}$  at 16 MeV, this corresponds to 10 Ci (370 GBq) at 50  $\mu\text{A}$  of prompt neutrons incident on the shielding walls, where absorption by  $(n,\gamma)$  reactions sets up a similar 10 MeV capture-gamma flux that overwhelms most attempts at energy-resolved gamma spectroscopy. At the University of Wisconsin RDS 112 site, a  $\text{LaBr}_3$  (2.54 cm  $\times$  2.54 cm (1 in  $\times$  1 in) in diameter) detector shielded in a 200 kg Pb collimator observes the target at 8 m through a 1  $\mu\text{sr}$  aperture, and is overwhelmed by pileup at any currents above 10  $\mu\text{A}$ . Nonetheless, the gamma spectrometer does find use in identifying the signature decay gamma during a brief halt after a few minutes into the irradiation, thus verifying that the target conditions are correct.

A more practical gamma detector is simply a wall-mounted scintillator, either a scrap of  $\text{CdWO}_4$  intensifier screen or organic, covering the active photocathode area of a side-window photomultiplier tube operated in the current mode. The linearity of this characteristic signal with beam current is a constant indicator that conditions are under control at the target.

A similar ‘peace-of-mind’ monitor is provided by the  $\text{BF}_3$  neutron detector (a so-called ‘long counter’). With a  $10^{-4}$  event/neutron incident sensitivity, this

detector is actually located in an adjoining cyclotron utility room, observing neutrons passing through a floor conduit to throttle event rates. The long counter has excellent intrinsic n- $\gamma$  discrimination, so that the ratio of the measured neutron to gamma flux from the two detectors further corroborates the beam target conditions. Needless to say, the use of neutron counting requires some forethought in choosing materials for collimators, foils, grids and target bodies (e.g. Ta) to achieve some degree of neutron silence when the target is filled with H<sub>2</sub><sup>16</sup>O.

## REFERENCES TO SECTION 2

- [2.1] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Principles and Practice, Technical Reports Series No. 465, IAEA, Vienna (2009).
- [2.2] WESTERN, J.L., Mechanical Safety Subcommittee Guidelines for Design of Thin Windows for Vacuum Vessels, Fermilab Report No. TM-1380, Fermi National Accelerator Laboratory, Batavia, IL (1991).
- [2.3] SCHLYER, D.J., FIROUZBAKHT, M.L., GARCIA, I., FERRIERI, R.A., “Correlation of hole size in support windows with calculated yield strengths”, Proc. on the Application of Accelerators in Research and Industry: No. 392 (DUGGAN, J.L., MORGAN, I.L., Eds), AIP Press, New York (1997) 1363–1365.
- [2.4] NICKLES R.J., A high-pressure gas target for cyclotrons, Nucl. Instrum. Meth. **177** (1980) 593–594.
- [2.5] BARNHART, T.E., et al., Water-cooled grid support for high-power irradiation with thin target windows, Appl. Radiat. Isotopes **58** (2003) 21–26.
- [2.6] NICKLES, R.J., DAUBE, M.E., RUTH, T.J., An <sup>18</sup>O<sub>2</sub> target for the production of <sup>18</sup>F<sub>2</sub>, Appl. Radiat. Isotopes **35** (1984) 117.
- [2.7] TAKÁCS, S., et al., Validation and upgrading of the recommended cross section data of charged particle reactions used for production of PET radioisotopes, Nucl. Instrum. Meth. B **211** (2003) 169–189.
- [2.8] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods, Technical Reports Series No. 468, IAEA, Vienna (2009).
- [2.9] BERRIDGE, M.S., VOELKER, K.W., BENNINGTON, B., High-yield, low-pressure [<sup>18</sup>O]water targets of titanium and niobium for F-18 production on MC-17 cyclotrons, Appl. Radiat. Isotopes **57** (2002) 303–308.
- [2.10] HONG, B.H., HUR, M.G., Double-grid [<sup>18</sup>O]water target for high yield of [<sup>18</sup>F]fluoride production on KIRMAS-13, Nucl. Instrum. Meth. B **241** (2005) 732–734.
- [2.11] POLICRONIADES, R., et al., F-18 production by means of <sup>20</sup>Ne(d,<sup>4</sup>He) reaction at ININ, Rev. Mex. Fis. **54** Suppl. 1 (2008) 46–49.
- [2.12] LAMBRECHT, R.M., NEIRINCKX, R., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals — XXIII: Novel anhydrous <sup>18</sup>F-fluorinating intermediates, Appl. Radiat. Isotopes **29** (1978) 175–183.

- [2.13] HELUS, F., et al., Contribution to the cyclotron targetry, *J. Radioan. Nucl. Ch.* **198** (1995) 247–252.
- [2.14] NICKLES, R.J., A shotgun approach to the chart of the nuclides, Radiotracer production with an 11 MeV proton cyclotron, *Acta Radiol. Suppl.* **376** (1991) 69–71.
- [2.15] SAJJAD, M., LAMBRECHT, R.M., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals XXXVI: investigation of some excitation functions for the preparation of  $^{15}\text{O}$ ,  $^{13}\text{N}$  and  $^{11}\text{C}$ , *Radiochim. Acta* **38** (1985) 57.
- [2.16] SAJJAD, M., LAMBRECHT, R.M., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals XXXIV: excitation function for the  $^{15}\text{N}(p,n)^{15}\text{O}$  reaction, *Radiochim. Acta* **36** (1984) 159.
- [2.17] TÁRKÁNYI, F., et al., Excitation functions of (p,2n) and (p,pn) reactions and differential and integral yields of  $^{123}\text{I}$  in proton induced nuclear reactions on highly enriched  $^{124}\text{Xe}$ , *Appl. Radiat. Isotopes* **42** (1991) 221–228.
- [2.18] LLOP, J., et al., Synthesis of S- $^{13}\text{N}$ ]nitrosoglutathione ( $^{13}\text{N}$ -GSNO) as a new potential PET imaging agent. *Appl. Radiat. Isotopes* **67** (2009) 95–99.
- [2.19] KOVÁCS, Z., et al., Excitation functions for the formation of some radioisotopes of rubidium in proton induced nuclear reactions on  $^{\text{nat}}\text{Kr}$ ,  $^{82}\text{Kr}$  and  $^{83}\text{Kr}$  with special reference to the production of  $^{81}\text{Rb}$  ( $^{81\text{m}}\text{Kr}$ ) generator radionuclide, *Appl. Radiat. Isotopes* **42** (1991) 329–335.
- [2.20] SUMIYA, L.C., SCIANI, V., Evaluation of irradiation parameters of enriched  $^{124}\text{Xe}$  target for  $^{123}\text{I}$  production in cyclotrons, *Appl. Radiat. Isotopes* **66** (2008) 1337–1340.
- [2.21] ENGELMANN, C., Contribution a l'étude de la détermination de Be, B, C, N, O et F par activation au moyen de p, d,  $^3\text{He}$  et  $\alpha$ , *J. Radioan. Nucl. Ch.* **7** (1971) 89–101.

### 3. WATER TARGETS — OPERATIONAL CONSIDERATIONS

Water targets are the most commonly used targets for the production of PET radionuclides, with  $^{18}\text{F}$  being the most popular radionuclide by far. The other water target commonly used is for the production of  $^{13}\text{N}$ . Since the main difference in these two targets is whether the water is enriched in  $^{18}\text{O}$  or not, the problems and considerations are very similar. One major difference is that the production of  $^{13}\text{N}$  is much more forgiving in the choice of target body materials than is the production of  $^{18}\text{F}$ .

#### 3.1. OVERPRESSURE AND SEALED CONDITIONS

The water target is usually run in one of two conditions. The first is with an overpressure of an inert gas such as helium and the second is with the target sealed such that the pressure inside the target is determined by the pressure that builds up in the target during irradiation. One limitation of pressurization with an inert gas in the target is that an initial amount of non-condensable gas exists, which mixes with the liquid and vapour during irradiation. Even a small component of non-condensable gas produces a dramatic decrease in heat transfer at a condensing surface [3.1].

The other method is to fill the target volume completely with water and then either pressurize the target with additional water, or seal it off completely and let it attain its own equilibrium pressure with the beam on. This method is intended to better utilize the effective heat transfer area in the condensing region of the target volume by eliminating the presence of non-condensable gas. There is some discussion as to which is better, but in either case, the additional pressure raises the boiling point of the water and increases the temperature differential between the target water and the cooling water, and therefore increases the efficiency of the thermal transfer. The target will be boiling in any case, as has been shown in several studies [3.2–3.5]. The boiling action and phase transition from liquid to gas inside the target both help with heat removal in the enclosed space. There is some controversy as to whether the boiling action just helps with the convective heat transfer or whether the phase transition also contributes a significant amount to the heat removal [3.1]. This depends, to a great extent, on the material used in the target body, as shown in the following sections. In any case, the steam created during boiling must be condensed to keep the liquid density in the target.

A diagram showing a target designed to accommodate the boiling action of the target is presented in Fig. 3.1 [3.6]. The target cavity of the [ $^{18}\text{O}$ ] water target

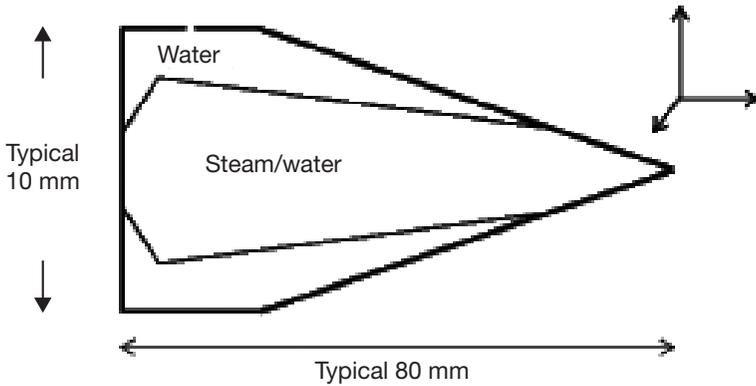


FIG. 3.1. Schematic diagram of water target design taking into account the boiling during irradiation.

design is illustrated. The typical size of the target is 80 mm deep and 10 mm wide. A schematic extent of an assumed steam/water matrix (steam/water) is also shown. There is water in the rest of the cavity.

An alternative to the static target is the recirculating water target [3.7]. For power levels above 3 kW, boiling batch targets with local cooling can become impractical due to excessive volumes of  $^{18}\text{O}$  water. One potential solution is a recirculating target system, in which the target water velocity is sufficient to prevent boiling [3.8, 3.9]. This target requires a larger volume of water, but the water is circulated through an external heat exchanger during irradiation to remove the heat. A diagram of this target is shown in Fig. 3.2.

In general, these recirculating targets have not come into routine use. The production capability of the static target is usually sufficient for most production requirements, and the added complexity of the recirculating target may result in more production failures.

### 3.2. TARGET GEOMETRY AND CONFIGURATION

The production capacity of any water target system is a function of beam energy and current. The heat generated in the water as the beam slows must be dissipated in some way, and there have been many different target geometries to optimize the heat removal. A simplified target drawing is included to highlight these features (Fig. 3.3). The target chamber shown has a racetrack shape. This has been the geometry of choice for many boiling water targets. It is intended to

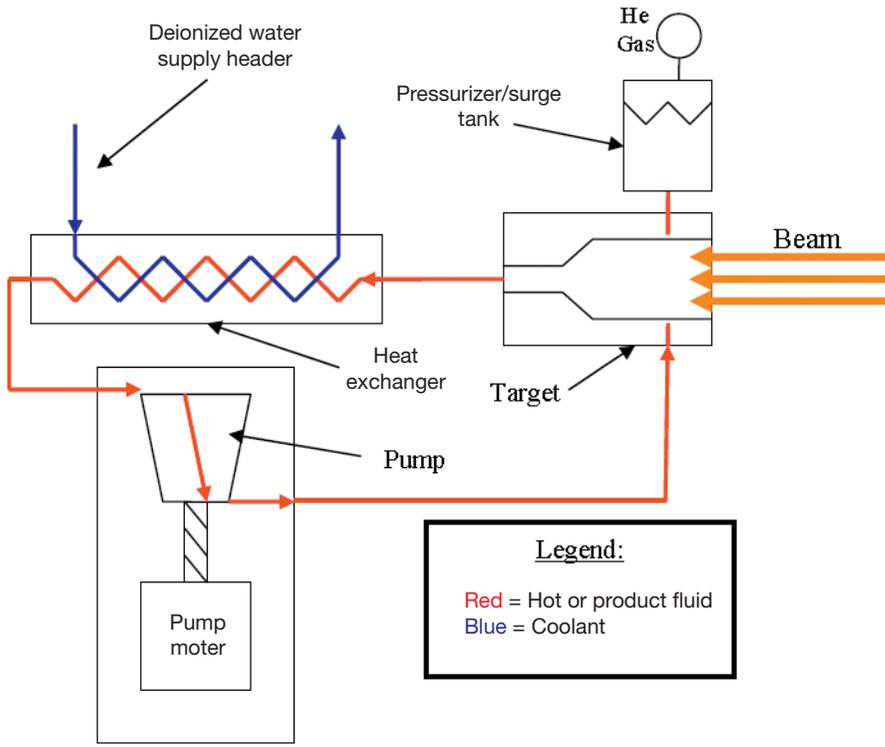


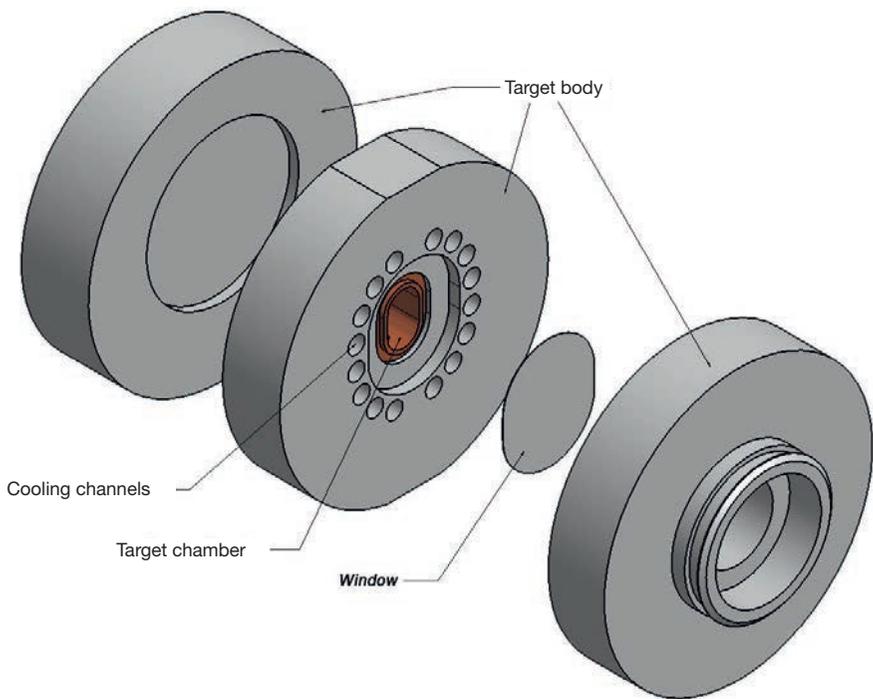
FIG. 3.2. General transfer scheme for a recirculating water target.

accommodate boiling in the lower region of the chamber, where the beam enters the target. The area above the beam strike provides a vapour space, or condenser.

### 3.2.1. 'Keyhole' target

One of the older designs for water targets is the keyhole design shown in Fig. 3.4. It is similar to the racetrack target design, but has a smaller area for condensation. This target design was usually run completely full of water. The space above the main target volume was for expansion and condensation of the water boiling in the target.

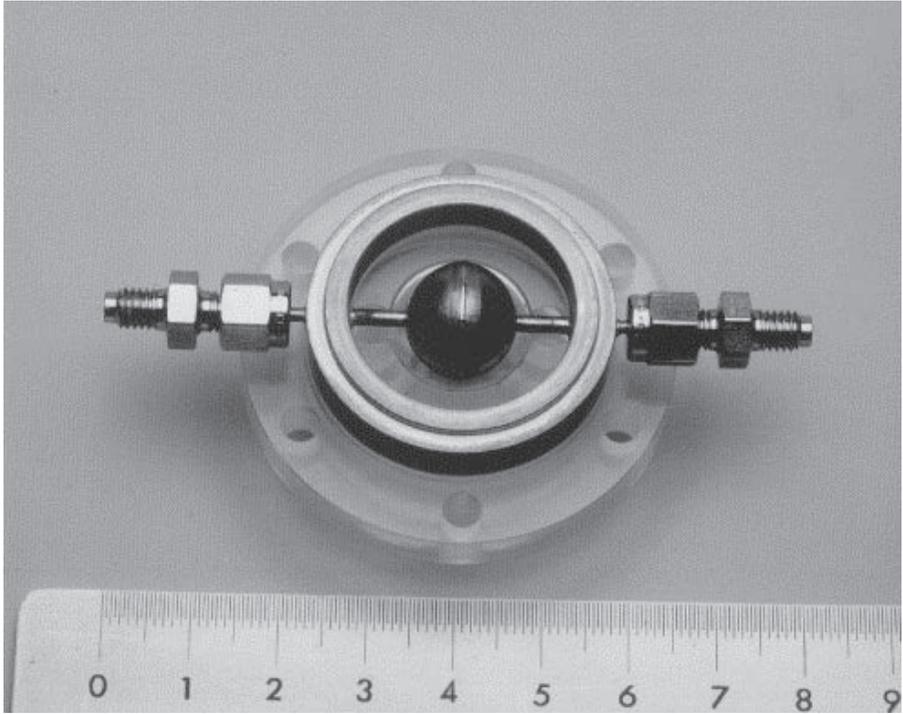
These target designs could be run either with an inert gas overpressure or closed off. This geometry has been utilized in both traditional reflux and thermosiphon targets [3.10].



*FIG. 3.3. Racetrack shaped target cavity for production of  $^{18}\text{F}$  from  $^{18}\text{O}$  enriched water.*



*FIG. 3.4. Keyhole water target design. The material of construction of this target was silver.*



*FIG. 3.5. Spherical niobium target which can contain very high pressures.*

### **3.2.2. Spherical target**

Another target system for the routine production of [ $^{18}\text{F}$ ]fluoride from  $^{18}\text{O}$  enriched water has been constructed [3.11]. It consists of a small spherical niobium target chamber mounted into a special holder, which provides rapid cooling by water flow around the sphere (Fig. 3.5). This system is operated without external overpressure and has been tested for beam currents up to  $50\ \mu\text{A}$ , with yields that are consistent and linear. The advantage of this design is that it can withstand very high internal pressures. For a tensile strength of  $3.3 \times 10^8\ \text{Pa}$  (soft niobium) and the dimensions specified above, this spherical target should be able to withstand an internal pressure of approximately  $2.53 \times 10^7\ \text{Pa}$ . Although this does not take into account any welded joints and the lowering of the tensile strength of the niobium at elevated temperatures, it shows that the predicted stability of the target chamber exceeds the regular operating pressure by more than one order of magnitude.

### 3.3. FOIL THICKNESS AND ENERGY ON THE TARGET

All gas and liquid targets have a least one ‘target foil’ that serves to separate the target material from the vacuum of the cyclotron. These foils are necessary and very often critical components for target performance. The foils should transmit all beam current hitting the target, and will correspondingly get both hot and radioactive. On some cyclotrons, the target foils are cooled by a stream of helium gas circulated between a vacuum isolation foil and the proper target foil. However, with advances in target design and beam control, this helium cooler scheme seems to be less widely used.

The energy loss in the foil(s) is a consideration, since this will have an impact on the beam energy and also on the heat that is deposited in the foil and transmitted into the target. The energy degradation relates to the stopping power of the foil material. The ideal situation is to have a foil that is as thin as possible, so that the minimum amount of energy is deposited in the foil, and yet thick enough so that it will withstand the pressure in the target during irradiation. An exception to this rule arises when it is necessary to reduce the beam energy in order to have the energy incident on the target material at an optimum level with respect to the cross-section of the desired nuclear reaction. In this case, it will often be advantageous to separate the main part of the energy loss in a separately cooled ‘energy degrader’ foil, in order to avoid excessive heating of the foil facing the target material.

For liquid and gas targets, a high working pressure will often be necessary for better performance at high beam currents and high production rates. High pressures call for relatively thick target foils of high strength; however, a thick foil that is not sufficiently cooled can easily heat during bombardment, leading to loss of tensile strength, and ultimately target failure. A hot front foil may also lead to unnecessary heating of target liquid or gas and unwanted chemical reactions between the foil and target material. The right choice of front foil is of ultimate importance for high current liquid or gas targets. The manufacturer’s recommendations for foils should normally be strictly observed.

As a charged particle moves through the surrounding medium, it interacts through ionization, scattering, various types of radiation losses, and least, but not insignificantly, by nuclear reactions. At energies typical for radioisotope production, a particle will undergo more than a million collisions before it comes to rest. Of course, the type of collisions and the exact path of an individual particle cannot be predicted. However, since the probabilities can be calculated and the number of particles is large, the overall behaviour of the beam can be predicted with high accuracy and reliability.

### 3.3.1. Stopping power

The slowing (loss of kinetic energy) of a charged particle is called the stopping power and is defined as:

$$\text{Stopping power } S(E) = -dE/dx \quad (1)$$

where

$E$  is the particle energy (MeV);

and  $x$  is the distance travelled (cm).

In many texts and tabular references, the linear length  $dx$  is replaced by the density weighted  $\rho dx$  (in  $\text{g/cm}^2$  or  $\text{mg/cm}^2$ ). In this case, we talk about mass stopping power, but calculations proceed as below, except that the foil thicknesses should also be inserted as density weighted.

The exact calculation of this quantity is complex but a reasonable approximation may be obtained rather easily [3.12].

The range of a charged particle through the absorber medium is just the integral of the energy loss equation. This gives the range ( $R$ ):

$$R = \int_0^{E_{\max}} \frac{1}{S(E)} dE \quad (2)$$

where

$S(E)$  is the stopping power at energy  $E$ ;

and  $E_{\max}$  is the maximum energy.

If the simplified energy loss equation is used with some basic assumptions, then the range relationship may be numerically integrated to energies of 0.1 MeV energy as:

$$R = \sum_0^{E_{\max}} \frac{1}{S(E)} \Delta E \quad (3)$$

Substituting the relevant physical constants into the equation:

$$R = \sum_0^{E_{\max}} \frac{AE}{144z^2Z \ln\left(\frac{2195E}{I}\right)} \Delta E \quad (4)$$

where

- $z$  is the particle  $z$  (amu);
- $Z$  is the absorber  $Z$  (amu);
- $A$  is the atomic mass of the absorber (amu);
- $E$  is the energy (MeV);
- $\Delta E$  is the energy interval (e.g. 0.1 MeV);

and  $I$  is the absorber effective ionization potential (eV).

This relation can be easily programmed on a personal computer, or even on some pocket calculators, to give a reasonable approximation of the range in a particular target material. The stopping power and ranges can also be obtained even more easily, using a freely available program called SRIM (The Stopping and Range of Ions in Matter). SRIM is a group of programs that calculates the stopping power and ranges of ions in matter using a quantum mechanical treatment of the collisions. The latest version can be downloaded from the SRIM site (<http://www.srim.org/>). The National Institute of Standards and Technology (NIST) maintains another good database of stopping powers for protons in elements and some mixtures. The NIST database can be simpler to use, if only the decremental energy loss in the foil is sought. The SRIM program can simulate the entire target comprising foils, a possible helium cooler, the target material itself and the target back, and can give important information about energy spread and transverse migration of a beam during the energy degradation.

### 3.3.2. Energy loss for typical foil materials

The typical target foil materials that will be considered here are aluminium, titanium, Havar and niobium. The results for aluminium and Havar are given in Tables 3.1 and 3.2. The ranges for the other materials can be easily determined using the range energy curves. The energies given here were calculated based on the SRIM computer program range curves.

In the case of an aluminium foil, the thickness tends to be from about 0.25 mm up to about 1 mm. Table 3.1 gives the energy loss for foils of 0.125, 0.25

TABLE 3.1. ENERGY OF PROTONS ON ALUMINIUM  
(DENSITY = 2.71 g/cm<sup>3</sup>)

Foil thickness (cm)	$E_{in}$ (MeV)	$E_{out}$ (MeV)	$\Delta E$ (MeV)
0.0125	19.0	18.3	0.7
	17.5	16.75	0.75
	16.5	15.7	0.8
	13.0	12.05	0.95
	11.0	9.9	1.1
	10.0	8.8	1.2
0.0250	19.0	17.5	1.5
	17.5	16.0	1.5
	16.5	14.85	1.65
	13.0	11.0	2
	11.0	8.7	2.3
	10.0	7.45	2.55
0.050	19.0	16.0	3
	17.5	14.3	3.2
	16.5	13.1	3.4
	13.0	8.7	4.3
	11.0	5.7	5.3
	10.0	3.8	6.2

$E_{in}$  = energy input;  $E_{out}$  = energy output;  $\Delta E$  = energy difference.

and 0.5 mm thickness. Values for foils of other thicknesses can be calculated from the output of the SRIM range energy tables.

In the case of a Havar foil, which is a much stronger and denser material, the foils are much thinner. Table 3.2 presents values for foils of common thicknesses for cyclotron liquid targets.

While aluminium foils only activate transiently during bombardment, and, thus, normally do not pose any significant radiation risk during service, the long term activation of Havar is very significant, and these irradiated Havar foils should be handled with care.

TABLE 3.2. ENERGY OF PROTONS ON HAVAR (DENSITY = 8.3 g/cm<sup>3</sup>)

Foil thickness (cm)	$E_{in}$ (MeV)	$E_{out}$ (MeV)	$\Delta E$ (MeV)
0.0125	19.0	18.8	0.2
	17.5	17.3	0.2
	16.5	16.3	0.2
	13.0	12.75	0.25
	11.0	10.7	0.3
	10.0	9.7	0.3
0.0250	19.0	18.65	0.35
	17.5	17.1	0.4
	16.5	16.1	0.4
	13.0	12.5	0.5
	11.0	10.45	0.55
	10.0	9.4	0.6
0.0500	19.0	18.3	0.7
	17.5	16.75	0.75
	16.5	15.7	0.8
	13.0	12.0	1.0
	11.0	9.85	1.15
	10.0	8.75	1.25

$E_{in}$  = energy input;  $E_{out}$  = energy output;  $\Delta E$  = energy difference.

### 3.4. PARAMETERS AND SENSORS TO MONITOR TARGET PERFORMANCE

Water targets are generally intended to produce <sup>18</sup>F(aq) fluoride from proton irradiation of H<sub>2</sub><sup>18</sup>O or <sup>13</sup>N-ammonia by proton irradiation of slightly ethanolic natural water. In the former case, the choice of target body materials is critical, to avoid ‘hard cations’ such as Fe<sup>2+</sup> or Al<sup>3+</sup>, which dictate the ‘quality’ or SN<sub>2</sub> labelling efficiency of the resulting fluoride. Different groups have preferred silver, niobium or tantalum. Table 3.3 qualitatively compares these materials with regard to several criteria.

The recent drop in cost for enriched <sup>18</sup>O water has relaxed the volume constraints somewhat, with most static targets now holding between 1 and 3 mL. However, the efficient removal of beam power makes the design of high power targets more complex than simply increasing the recess depth to accommodate

TABLE 3.3. WATER TARGET MATERIALS

Material	'Quality'	Maintenance	Conductivity	Machinability	Neutrons
Silver	Good	Fair	Highest	Excellent	Fair
Niobium	Excellent	Best	Fair	Fair	Fair
Tantalum	Excellent	Good	Poor	Fair	Excellent

any vapour voids. The more successful  $^{18}\text{O}$  water targets are gridded single foil target bodies, employing elevated pressure of 2.86–10.44 MPa (400–1500 psig) to push up the boiling point and to facilitate the gravitational convective currents that bring the equivalent kilowatt heat load to the top of the target, where the vapour phase recondenses in a small head space. A number of investigators have been pursuing forced convection, with recirculating flow loops of  $\approx 10$  mL pumped vigorously through the target, to a heat exchanger and anion exchange column for switched trap and release cycles (see Section 3.1). The performance of such a spatially separated system lends itself to a radiation detector next to the trapping column, which verifies the activity buildup characterizing a successful irradiation.

The ammonia target is more relaxed in material choice, with both aluminium and grade 316 stainless steel performing well for the direct production of  $^{13}\text{N}$ ammonia in the target. Five millimolar ethanol in sterile water is pumped through the target under irradiation, then passing to the hot cell for trapping on a strong cation exchange column. A NaI crystal attached to a photomultiplier tube operated in the current mode can verify the buildup of trapped  $^{13}\text{N}$ ammonia, reaching about 300 mCi (11.10 GBq) at 20  $\mu\text{A}$ , 16 MeV proton energy. Release of the  $^{13}\text{N}$ ammonia with 155 mM NaOH and titration with citrate-buffered HCl to pH7 results in an injectable  $^{13}\text{N}$ H<sub>3</sub> in saline after radiopharmaceutical workup.

The operating performance of cyclotron targets can be conveniently monitored by neutron and gamma spectroscopy during, and immediately following, irradiation. Far from an academic exercise, these measurements can reveal serious problems occurring within the target before they become evident at the EOB. Most radionuclides destined for PET application are the result of X(p,n)Y reactions, so that neutrons are the immediate, and inescapable consequence. Even (p, $\alpha$ ) reactions are generally accompanied by parallel (p,n) channels, as  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$  is accompanied by  $^{14}\text{N}(\text{p},\text{n})^{14}\text{O}$ , making neutron detection still reflective of target conditions. Actual neutron spectroscopy is a demanding discipline, with the energy derivable from time-of-flight spectra or n-gamma pulse shape discrimination with organic scintillators. This energy

information is not needed for cyclotron targetry diagnostics, so the detector characteristics are greatly simplified. Much more important is simplicity, robustness, intrinsic gamma insensitivity and, surprisingly, very low sensitivity in order to operate in close proximity to the target. Two detectors with these properties include:

- Fission proportional counters with sensitivities of the order of  $10^{-6}$ – $10^{-7}$  detected events per incident neutron;
- $^{10}\text{BF}_3$ -loaded proportional counters, with a moderator known as a ‘long counter’.

Both of these counters have near perfect gamma discrimination and need only minimal electronics (bias supply, pre-amp, amplifier and discriminator) to provide kilohertz counting rates inside the cyclotron bunker environment near the target producing  $10^{10}$ – $10^{11}$  neutrons/s. Several attempts to efficiency calibrate the detector with a  $^{241}\text{Am}/\text{Be}$  source of known neutron intensity have been unable to quantitate the absolute neutron flux to better than a factor of two, doubtless a consequence of the harder neutron spectrum from  $^{241}\text{Am}/\text{Be}$  than the fission spectrum from typical (p,n) reactions.

Two gamma detectors are in routine use in some laboratories, a simple  $\text{CaWO}_4$  scintillator X ray screen wrapped around a side-window photomultiplier operated in the current mode, and a  $\text{LaBr}_3$  scintillator viewing the target with a  $1\ \mu\text{sr}$  solid angle through a 200 kg lead collimator at a 5 m distance from the target. Even with this shielding and distance, the prompt gamma spectrum is lost to pileup at typical operating beam currents, but the activation products are identifiable with the beam off. Between the neutron and gamma rates, each reaction is readily identified, and simple problems such as an empty target, or the wrong nickel isotopic target, can be immediately spotted and corrected.

### 3.5. HEAT TRANSFER IN LIQUID TARGETS

Several modes of heat transfer are operational in liquid targets. These include convective heat transfer of the heat generated by the beam in the target water to the walls of the target chamber, convective heat transfer at the rear of the target chamber into the cooling water and conductive heat transfer from the water in the target chamber through the rear wall to the cooling water interface. There is also phase transition heat transfer in the target water as it boils inside the target chamber. Figure 3.6 shows the boiling of the water during irradiation at 5 and  $10\ \mu\text{A}$ . This demonstrates that phase transitions are occurring in the target under certain conditions.

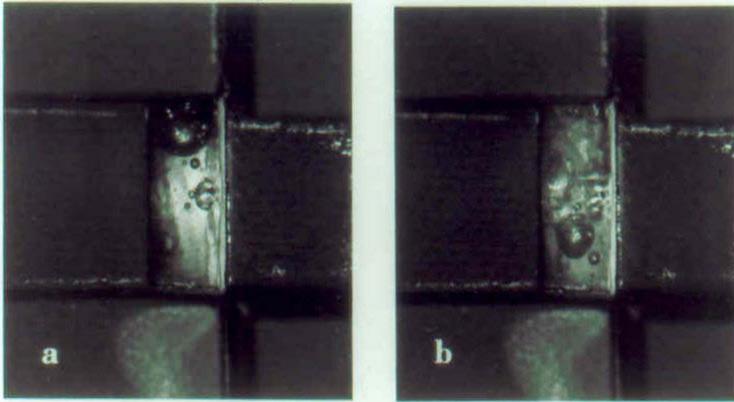


FIG. 3.6. Boiling in the water target during irradiation at  $5 \mu A$  (a) and  $10 \mu A$  (b).

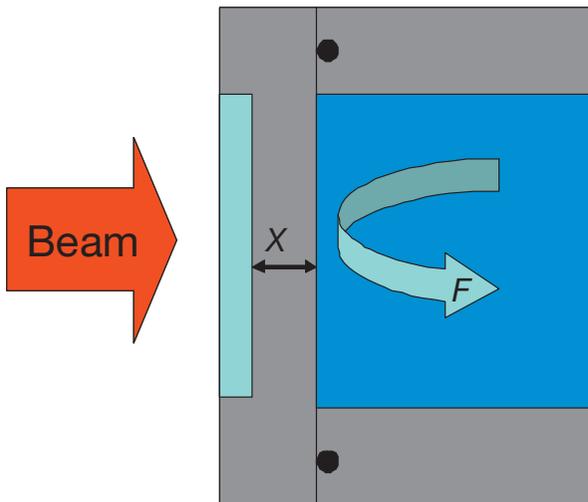


FIG. 3.7. Simple diagram showing the model used for conductive heat transfer.

Calculations were carried out for the conduction of heat through the rear wall to the cooling water interface to examine the effect of the metal used for the target body on the relative contributions of these modes of heat transfer.

### 3.5.1. Model used for conduction calculations

Several assumptions were made in these calculations. The first was the size of the target and the second was that the cooling water flow would not be limiting in the removal of the heat from the target; that is to say that the convective heat transfer at the rear of the target would be significantly greater than the conductive heat transfer through the rear wall. A simple diagram of the model calculations is shown in Fig. 3.7.

In this model, the distance  $X$  is the thickness of the rear wall and the cooling water flow ( $F$ ) is assumed to be an infinite heat sink. Equation (5) is used to calculate the heat transfer:

$$Q = \frac{\kappa A \Delta T}{d} \quad (5)$$

where

- $Q$  is the heat transferred;
- $A$  is the area of heat transfer;
- $\kappa$  is thermal conductivity;
- $d$  is distance ( $X$  in Fig. 3.7);

and  $\Delta T$  is temperature differential in K.

Calculations of the heat transfer were carried out for the four common target materials of silver, tantalum, niobium and titanium. The other assumptions that were made were that there was a constant heat load and that there was a 15 MeV beam of 30  $\mu\text{A}$ , which results in a heat load of 450 W. If the beam current or beam energy is lower, then the total heat load will be lower. An example calculation is shown here. A layer of silver ( $\kappa = 4 \text{ W}\cdot\text{cm}^{-1}\cdot\text{K}^{-1}$ ) 5 mm thick between the target water at 100°C and the cooling water at 25°C is assumed. The area for heat transfer is a circle of 2 cm diameter ( $A = 3.14 \text{ cm}^2$ ):

$$Q = \frac{\kappa A \Delta T}{d}$$

$$Q = (4)(3.14)(75)/(0.5)$$

$$Q = 1880 \text{ W}$$

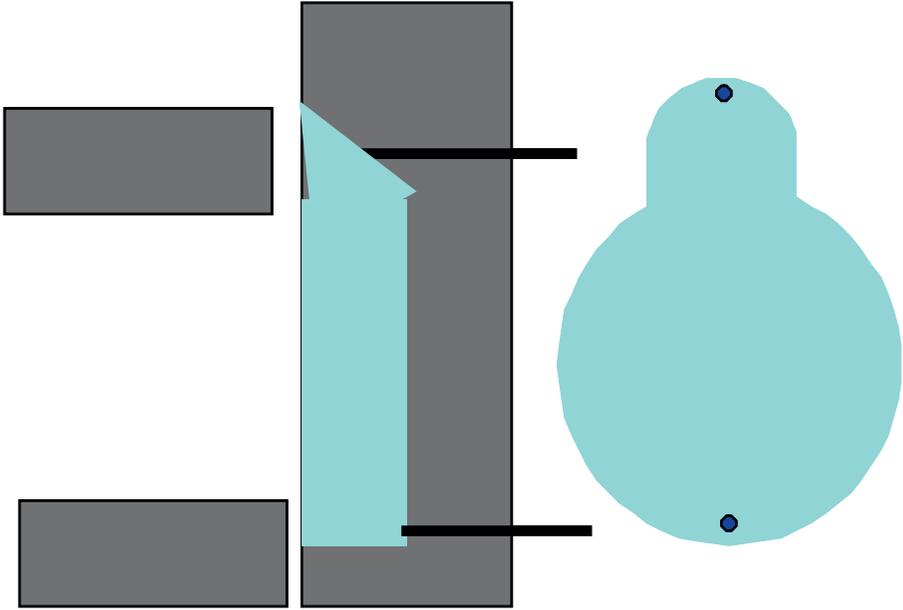


FIG. 3.8. Schematic diagram of the water target with the space for condensing the water above the target volume.

Thus, for the silver target, the heat transfer through the back wall is sufficient to cool the water under these conditions.

### 3.5.2. Model used for phase transition calculations

In this model, it was assumed that one third of the water in the target was being vaporized by the beam during a 1 s interval. The water is then condensed quickly by a cold volume immediately above the target. This water is then returned to the target volume to be vaporized again. A model of the target volume is shown in Fig. 3.8.

The equation for heat transfer is given by the equation:

$$Q = m\Delta H_{\text{vap}} \quad (6)$$

where

$m$  is the mass of the fluid being vaporized;

and  $\Delta H_{\text{vap}}$  is the heat of vaporization.

In a sample calculation where it is assumed that the target holds 2.0 mL of water and one third of the water boils in the lower volume and then condenses in an upper volume:

$$Q = m\Delta H_{\text{vap}}$$

$$Q = (0.66)(2260)$$

$$Q = 1492$$

In this example, the heat removed by vaporization is more than enough to remove the heat from the target.

The thermal conductivities of the typical target materials are given in Table 3.4.

If the thickness of the rear wall for the four target materials is plated, the point where the conduction pathway is able to remove the heat being deposited by the beam is seen. This is shown in Fig. 3.9.

The graph shows that, in all cases, conduction through the rear wall of the silver target is able to remove the entire heat load on the target. It also shows that a niobium or tantalum target with a rear wall thickness of less than 3 mm will be able to remove the heat load. In no case was the conduction pathway sufficient in the titanium target.

For the phase transition pathway, the amount of heat removed is directly proportional to the volume of the water being vaporized. In all of these calculations, it was assumed that the water vaporization occurred in 1 s. If the time to vaporize increases, the amount of heat removed is reduced proportionally. The results for different target volumes are shown in Fig. 3.10. In all cases, it was assumed that one third of the water was vaporized during a 1 s period.

TABLE 3.4. THERMAL CONDUCTIVITIES OF TYPICAL WATER TARGET MATERIALS

Element	Thermal conductivity ( $\text{W}\cdot\text{cm}^{-1}\cdot\text{K}$ )
Silver	4.0
Tantalum	0.54
Niobium	0.53
Titanium	0.21

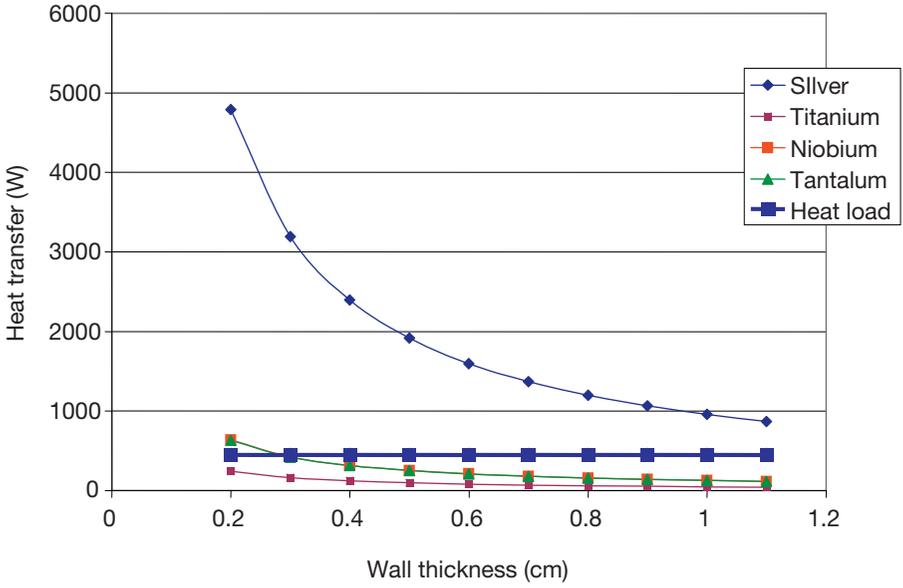


FIG. 3.9. Heat transfer by conduction in four types of metal water target.

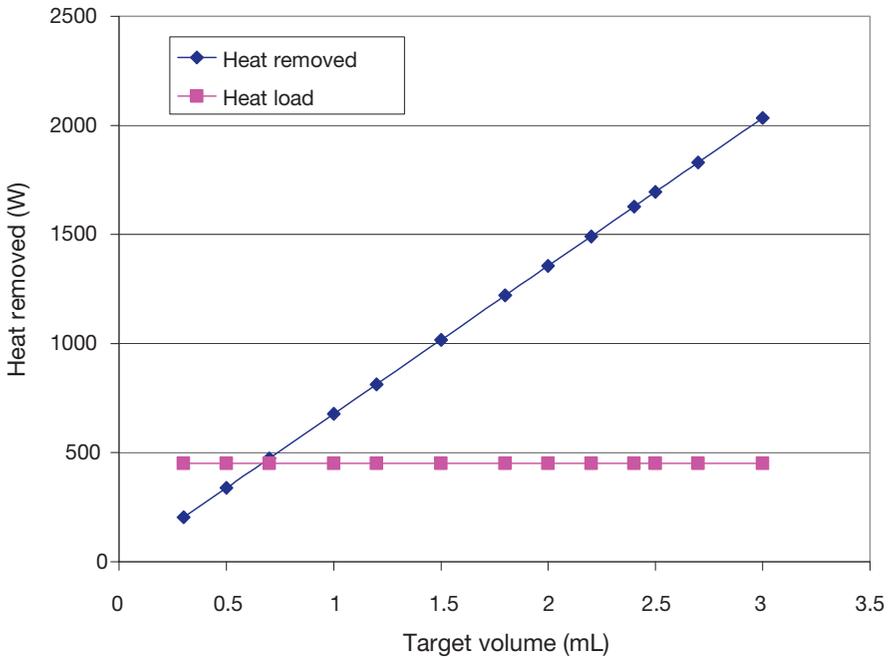


FIG. 3.10. Heat removed by boiling of target water as a function of target volume.

It is easy to see that target volumes greater than 0.7 mL are capable of removing the heat load under the conditions specified. The specific heat for water is  $4.186 \text{ J}\cdot\text{g}^{-1}\cdot\text{K}^{-1}$ . Since 1 J is 1 W·s, the specific heat capacity is  $4.186 \text{ W}\cdot\text{s}\cdot\text{g}^{-1}\cdot\text{K}^{-1}$ . To raise the temperature of 1 g of water by 100 K in 1 s requires 419 W of power. Since this is close to the power being deposited by the beam, the assumption that the water can be vaporized quickly is somewhat reasonable.

### 3.5.3. Recommendation

The conclusion from this very simple study is that conduction is often insufficient to remove all of the heat generated as the beam stops in the target water. The heat transfer can be aided by a phase transition from the liquid phase to the gas phase (vaporization). This implies that if a niobium or tantalum target is used, the target should be designed specifically to take advantage of the phase transition cooling method. A volume above the beam strike area where the water can condense and return to target volume is recommended for these targets. A more detailed analysis of the heat removal has been carried out using finite element analysis [3.13, 3.14]. These methods are far more accurate, but usually require a commercial computer program to carry out the calculations.

## 3.6. SAFETY ISSUES — RADIATION EXPOSURE, INDUSTRIAL HYGIENE ISSUES, DUAL BEAM OPERATION

All of the commercially built H- or D-cyclotrons are equipped with the possibility to extract two beams simultaneously. In principle, this can be managed easily by two stripper foils, which in most cases are  $180^\circ$  apart from each other and are precisely adjustable radially. The method is based on the fact that the accelerated beam pulses have a radial extension. By keeping one foil fixed at the desired extraction energy, one can select a part of the total beam current just by slowly moving in the second foil. In addition, both foils have to be adjusted azimuthally, in order to meet the predicted target or beam line.

Even though these adjustments are easy, only a few radioisotope producers routinely use the dual beam method. One of the reasons might be that, in order to keep the intensity ratios constant, it is necessary to have a perfectly adjusted cyclotron and a good automatic control mechanism, based on the radial positioning of one of the foils and/or an adjustment of the harmonic coils.

For very high beam currents, there is always a small risk of destroying one of the targets if one of the stripping foils becomes damaged and, therefore, one of

the targets receives the entire beam current from the cyclotron. No interlock system is fast enough to avoid this problem.

With the development of water targets operating at currents up to 150  $\mu\text{A}$  for many of the existing compact cyclotrons, operating with a dual beam with a maximum of 150  $\mu\text{A}$  on two targets for larger scale FDG production seems not to be so crucial.

### 3.7. TARGET MAINTENANCE

The level of maintenance required in a water target is very much a function of the target body material. Silver targets are notorious for needing regular maintenance, while niobium water targets often go for years with no maintenance at all. The level of maintenance also differs depending on the particular cyclotron beam energy, beam current and frequency of production.

A routine maintenance procedure should be established and followed for the target processing and quality control. Table 3.5 gives a suggested schedule for maintenance [3.15].

The following sections present some common techniques for maintaining targets. These are based on a survey taken from several centres where routine production of  $^{18}\text{F}$  is carried out.

TABLE 3.5. SUGGESTED MAINTENANCE SCHEDULE FOR  $^{18}\text{O}$  WATER TARGETS

Frequency	Procedure
Weekly	Visually check for damaged tubing Leak test the system Prepare fresh $^{18}\text{O}$ water for use Blow the transfer lines clean and dry with nitrogen gas Replace any rubber seals on the system (e.g. Burrell seals)
Monthly	Test plastics for radiation damage Backflush valves and check operation Track target yields to establish trends
6 monthly	Clean target (more or less depending on target type — see below) Replace all foils Replace plastic parts if there is any degradation
General	Refrigerate $^{18}\text{O}$ water Use sterile needles

### 3.7.1. Silver target

Several methods have been described for cleaning the silver target. The usual frequency of these maintenance procedures is about once every 6 months, under regular usage. The following is a list of the various procedures:

- Clean with strontium carbonate and isopropyl alcohol followed by a deionized water rinse in an ultrasonic bath.
- Clean the silver body using two parts sodium bicarbonate and one part pure ethanol; scrub with cotton swabs until something approaching a mirror finish is restored to the silver.
- Buff the silver chamber with baking soda in isopropanol; ultrasonicate in water; air dry; replace all foils and O-rings and metal seals.
- Scrub with baking soda/methanol, followed by extensive water washing.
- Clean the inside surfaces of the target with acetone and water, dry thoroughly and rebuild with new foils and O-rings.
- Make a slurry using sodium bicarbonate and methanol. Clean the target with a cotton swab dipped in sodium bicarbonate/methanol slurry. Rinse with Milli-Q water. Allow the target to air dry. Pull the target assembly from the cyclotron and disassemble. Pour enough cleaning solution into the sonicator to cover the target and sonicate as follows: chloroform for at least 10 min; acetone for at least 10 min; methanol for at least 10 min; Milli-Q water for at least 10 min. Check the radiation level of each used cleaning solution with a survey meter. Pour the waste into labelled radioactive waste containers, in the cyclotron vault, and allow to decay to background before disposal. Dry the target parts in a drying oven. Reassemble with a clean target and with the water target maintenance kit. Fill out a target cleaning record sheet. Reinstall the target on the cyclotron. Change the tubing lines to the hood. Check for leaks, using helium pressure and snoop (soapy water solution). Fill and flush the target and lines with Milli-Q water three times. Do 1–2 short bombardments. Collect and check the water's colour, pH and volume. Check the level of radioisotope impurities prior to use.

As can be seen from this list, the procedures can vary considerably but, in general, the best is to clean with baking soda/alcohol slurry on a cotton swab, followed by thorough rinsing with water and air drying. Doing one or two practice runs with distilled water is also recommended, to ensure that any residue in the target is washed out before resuming normal production.

### 3.7.2. Niobium or tantalum targets

The maintenance schedule for niobium or tantalum targets is much less stringent. It is not uncommon for the target to go for years without maintenance. If maintenance is required, the following procedures are common:

- If the target looks dirty, wash overnight with phosphoric acid (0.1 M); rinse with water; then dry overnight.
- Change the windows and O-rings, clean the target if necessary and change the transfer lines every 6 months.
- Replace windows every 6 months and lines every year; the cavity is rinsed with ethanol with no further cleaning.
- Replace the windows and O-rings, cleaning inside with ethanol every 6 months.

The conclusion from most centres is that the niobium target is superior to the silver target in the fact that essential maintenance is less frequent.

### 3.7.3. Titanium targets

There is little information on titanium targets, since they have fallen out of favour in most centres. They seem to have slightly lower yields than either the silver or niobium targets and require some routine maintenance in the form of cleaning in the same manner as the silver targets. It has also been noted that the yield from these targets decreases steadily with time.

## 3.8. TARGET STORAGE CONDITIONS (WET VERSUS DRY)

The  $^{18}\text{O}$  water target is normally emptied just after the EOB. This is done by using a comparatively small helium gas overpressure to push the irradiated water through narrow bore tubing to the relevant hot cell/chemistry module. The transfer sequence is normally of short duration (at most a few minutes), in order to reduce the decay loss. Although this procedure will remove most of the target liquid from both the target chamber and transfer lines, it will not dry out the chamber or internal tubing surfaces completely.

These surfaces can be dried by applying a protracted helium flow (10–15 min) at the end of the transfer, either after the end of synthesis or by redirecting the target transfer line to a waste system just in front of the synthesis module. This will remove water and moisture from all surfaces, but not all remaining activity.

There is no single clear opinion as to whether the target and transfer lines should be dried after use or not. Clearly, if another bombardment is imminent using the same target and transfer tubing, no drying is necessary, as this will be a waste of time. If the target is taken out of production for many days, or perhaps removed for service, then it should be dried. However, very often the target will be used again the next day, and, in this case, there are opposing arguments as to the value of a drying procedure. On the one hand, it just adds to the complexity of operation. On the other, the removal of water could prevent the possibility of corrosion inside the target and lower the chance of adverse microbial growth in the target transfer system.

As for the corrosion argument, the drying could be of some value, especially if very high SA and high yields are sought. However, modern combinations of target body, foil and seal materials are very tolerant to continuous water contact, and daily drying might be unnecessary. On the other hand, residual activity left in the target and transfer system can add to the cumulative radiation damage to the tubing, thus justifying drying to increase the intervals between target line replacements.

Considering the risk of microbial growth, it is often stated that the target and target water are 'sterilized by radiation'. While this is true for the target water present in the target cavity itself during bombardment, it is not true for interior tubing and valve surfaces that are only in contact with the active, irradiated water. The activity levels handled will certainly lower the risk of microbial growth, but this procedure cannot be seen as a 'secure sterilization' in the pharmaceutical sense. At present, most radiochemical synthesis procedures will not transfer microbes or endotoxins to the final product to any significant degree, but the microbial growth could increase activity losses during transfer and possibly lower the labelling yield. In some production environments, the starting materials, including the target water, should preferentially be of 'low bioburden'. In these cases, proper drying of the transfer line is justified.

The above arguments provide no clear guidance on the choice of procedures. They can, however, help to outline the benefits of the different practices. Each production site must choose and specify operating conditions based on local conditions and requirements.

### REFERENCES TO SECTION 3

- [3.1] STEINBACH, J., et al., Temperature course in small volume [ $^{18}\text{O}$ ] water targets for [ $^{18}\text{F}$ ]F production, *Appl. Radiat. Isotopes* **41** (1990) 753–756.
- [3.2] HUR, M-G J., et al., The study of proton beam irradiated  $\text{H}_2^{18}\text{O}$  water target, *Nucl. Instrum. Meth. B* **241** (2005) 735–737.
- [3.3] HESELIUS, S.J., SCHLYER, D.J., WOLF, A.P., A diagnostic study of proton-beam irradiated water targets, *Appl. Radiat. Isotopes* **40** (1989) 663–669.
- [3.4] HESS, E., BLESSING, G., COENEN, H.H., QAIM, S.M., Improved target system for production of high purity [ $^{18}\text{F}$ ] fluorine via the  $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$  reaction, *Appl. Radiat. Isotopes* **52** (2000) 1431–1440.
- [3.5] NYE, J.A., AVILA-RODRIGUEZ, M.A., NICKLES, R.J., A grid-mounted niobium body target for the production of reactive [ $^{18}\text{F}$ ]fluoride, *Appl. Radiat. Isotopes* **64** (2006) 536–539.
- [3.6] GIVSKOV, A., JENSEN, M., “[ $^{18}\text{O}$ ]Water target design for production of [ $^{18}\text{F}$ ]fluoride at high irradiation currents”, Proc. 13th Int. Workshop on Targetry and Target Chemistry (WTTC), Copenhagen (2010).
- [3.7] IWATA, et al., [ $^{18}\text{F}$ ]Fluoride production with a circulating [ $^{18}\text{O}$ ]water target, *Appl. Radiat. Isotopes* **38** (1987) 979–984.
- [3.8] WIELAND, B., WRIGHT, B., “Regenerative turbine pump recirculating water target for producing F-18-fluoride ion with several kW proton beams”, Proc. 9th Int. Workshop on Targetry and Target Chemistry (WTTC), Turku (2002).
- [3.9] STOKEL, Y.M.H., et al., Deployment, Testing and Analysis of Advanced Thermosyphon Target Systems for Production of Aqueous [ $^{18}\text{F}$ ]Fluoride via  $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ , DOE, Washington (2008).
- [3.10] STOKEL, Y.M.H., et al., “High yield thermosyphon targets for production of  $^{18}\text{F}$ -fluoride”, Proc. 11th Int. Workshop on Targetry and Target Chemistry (WTTC), Cambridge (2006).
- [3.11] ZEISLER, S.K., et al., Water-cooled spherical niobium target for the production of [ $^{18}\text{F}$ ]fluoride, *Appl. Radiat. Isotopes* **53** (2000) 449–453.
- [3.12] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Principles and Practice, Technical Reports Series No. 465, IAEA, Vienna (2009).
- [3.13] GAGNON, K., WILSON, J.S., MCQUARRIE, S.A., “Thermal modelling of a solid cyclotron target using finite element analysis: an experimental validation”, Proc. 13th Int. Workshop on Targetry and Target Chemistry, Copenhagen (2010).
- [3.14] CHANG, C.T., KOJASOY, T.G., LANDIS, F., Confined single- and multiple-jet impingement heat transfer I: turbulent submerged liquid jets, *Int. J. Heat Mass Transfer* **38** 5 (1995) 833–842.
- [3.15] STEEL, C.J., DOWSETT, K., PIKE, V.W., CLARK, J.C., “Ten years’ experience with a heavily used target for the production of [ $^{18}\text{F}$ ]fluoride by proton bombardment of [ $^{18}\text{O}$ ]water”, Proc. 7th Int. Workshop on Targetry and Target Chemistry, Heidelberg (1997).

## 4. WATER TARGETS — PRODUCT CONSIDERATIONS

Fluorine-18 has been produced by a variety of nuclear reactions, using both nuclear reactors and accelerators. The target materials used can be either in the solid, liquid or gas phase. Recovery of  $^{18}\text{F}$  is different with each type of target material. An enriched  $^6\text{LiCO}_3$  solid target has been used for production of  $^{18}\text{F}$ . In this case, separation of  $^{18}\text{F}$  from the solid target was performed by absorbing the  $[^{18}\text{F}]$ fluoride on alumina or ion exchange resins, followed by thorough washing before  $[^{18}\text{F}]$ fluoride elution using basic solution [4.1].

Gas targets, in particular enriched  $^{18}\text{O}$  and  $^{20}\text{Ne}$ , are also used for the production of  $^{18}\text{F}$  via  $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$  and  $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$  nuclear reaction, respectively [4.2, 4.3]. Both target systems produce carrier-added  $^{18}\text{F}$  gas ( $^{18}\text{F}_2$ ) suitable for electrophilic radiofluorination reactions intended for applications where high SA is not required. The recovery of  $^{18}\text{F}$  from  $\text{F}_2$ -passivated gas targets is usually achieved in one of two ways: by adding  $^{18}\text{F}_2$  carrier to the neon target gas and releasing it into the synthesis chamber, or by mixing natural fluorine and noble gases to the target, followed by brief irradiation to induce isotopic exchange between the  $^{18}\text{F}$  adhering to the walls and the added  $^{18}\text{F}_2$  [4.4, 4.5]. These methods of recovery were successfully used in electrophilic radiofluorination reactions. For nucleophilic radiofluorinations,  $[^{18}\text{F}]$ fluoride was recovered by passing  $^{18}\text{F}_2$  gas through an ionic column, followed by elution with appropriate solution [4.6]. Another method is in situ conversion of  $^{18}\text{F}_2$  to  $[^{18}\text{F}]\text{H}$  under elevated temperature before proper trapping [4.7].  $[^{18}\text{F}]$ fluoride has also been trapped on a metal coated glass tube placed inside the target. This test tube is finally used for in situ nucleophilic radiofluorination reactions [4.8]. However, production of  $[^{18}\text{F}]$ fluoride from gas targets suffers from low specific activities and practical limitations.

### 4.1. $^{18}\text{F}$ RECOVERY WITH ION EXCHANGE

All high SA and no-carrier-added  $[^{18}\text{F}]$ fluoride is currently produced using enriched  $[^{18}\text{O}]$ water in a target chamber made of inert metal, such as silver, titanium, niobium or tantalum. To avoid an excess of water in radiofluorination reactions,  $[^{18}\text{F}]$ fluoride was previously recovered from enriched water using several different techniques. Among these are  $[^{18}\text{F}]$ fluoride electrochemical deposition, conversion to a gaseous phase before trapping, and enriched  $[^{18}\text{O}]$ water distillation [4.9, 4.10]. These techniques have some disadvantages, which limit their applications, and so most  $[^{18}\text{F}]$ fluoride isolation is done by means of an ion exchange resin column such as Dowex AG1-X8 [4.11]. Using an

ion exchange resin or quaternary methyl ammonium (QMA) anion exchange resin offers not only separation of [ $^{18}\text{F}$ ]fluoride and efficient recovery of enriched [ $^{18}\text{O}$ ]water, but also scavenging of many ion contaminants from the target or foil that can alter radiofluorination reactions. Fluorine-18 fluoride is subsequently recovered by rinsing the ion exchange resin column with a mixture of acetonitrile–water, containing weakly basic carbonates (in the form of potassium, rubidium or caesium), to yield [ $^{18}\text{F}$ ]fluoride with a recovery efficiency greater than 95% [4.11–4.13]. Similar procedures using quaternary ammonium resins allow the separation of [ $^{18}\text{F}$ ]fluoride from target water and also create a reactive nucleophilic environment for subsequent radiofluorination reactions [4.14, 4.15]. Commercial QMA anion exchange columns (QMA Sep-Pak) are routinely used for retaining several curies of [ $^{18}\text{F}$ ]fluoride and the recovery of enriched [ $^{18}\text{O}$ ]water for further reuse after appropriate purification. The retained [ $^{18}\text{F}$ ]fluoride can be eluted with an acetonitrile solution of cyclic crown ether (Kryptofix 222) or tetrabutylammonium salts and potassium carbonate [4.16–4.18] (Fig. 4.1). Since fluorine is the most electronegative element, the formation of a water ‘shell’ in an aqueous solvent dramatically decreases the [ $^{18}\text{F}$ ]fluoride reactivity. The recovered [ $^{18}\text{F}$ ]fluoride elution and its counter ions are usually azeotropically dried to remove any residual water, using an automated chemistry module before any nucleophilic radiofluorination reactions [4.19].

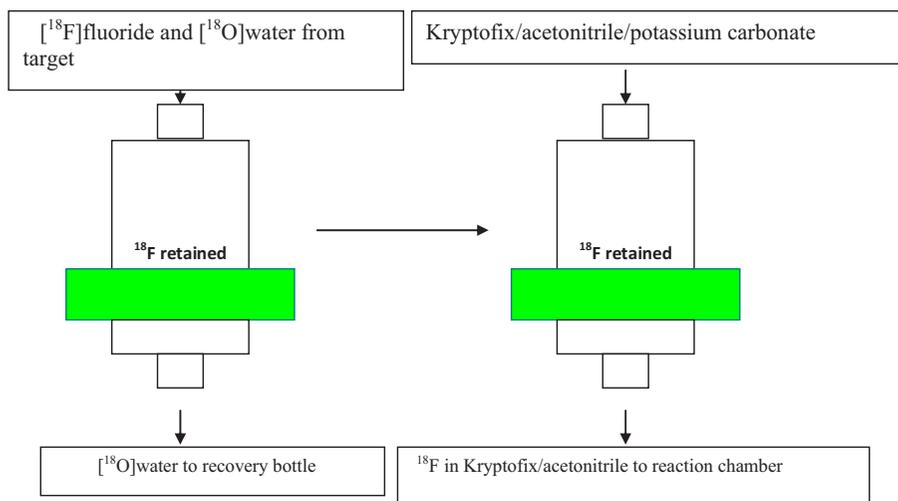


FIG. 4.1. Recovery of [ $^{18}\text{O}$ ]water and delivery of [ $^{18}\text{F}$ ]fluoride to the reaction chamber.

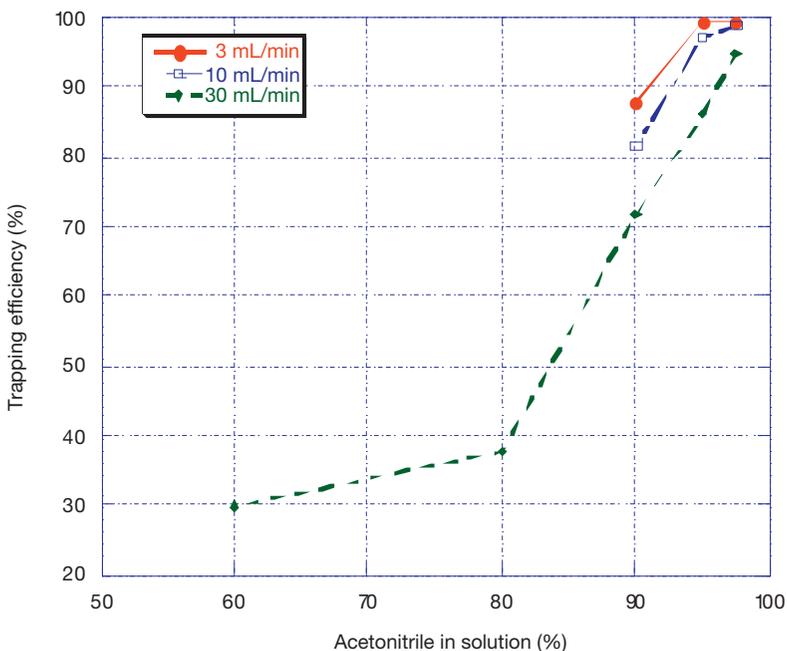


FIG. 4.2. QMA TE for  $^{18}\text{F}$  in acetonitrile/water/carbonate solutions.

The ability of a QMA Sep-Pak to trap [ $^{18}\text{F}$ ]fluoride, when in a solution of  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$  and  $\text{H}_2\text{O}$ , is strongly dependent on the  $\text{CH}_3\text{CN}:\text{H}_2\text{O}$  ratio. The flow rate is also a significant factor.

Figure 4.2 shows the trapping efficiency (TE) for a given flow rate, and for a given acetonitrile:water ratio. All samples contained 1 mL of water and 1 mg  $\text{K}_2\text{CO}_3$ . Thus, the samples that were 90% acetonitrile had a total volume of 10 mL. The TE rose as water concentration dropped and also with reduced flow rates.

The behaviour of long lived metal ions in a QMA Sep-Pak system is described in detail in Ref. [4.20]. A representative data set is shown in Fig. 4.3. The target was a niobium target body with a titanium foil, which results in the production of  $^{48}\text{V}$  from the  $^{48}\text{Ti}(p,n)^{48}\text{V}$  nuclear reaction. The curve shows the elution of  $^{18}\text{F}$  and  $^{48}\text{V}$  from a QMA Sep-Pak Light for aqueous  $\text{K}_2\text{CO}_3$  solutions of 0.5 and 3 mg/mL.

Reducing the carbonate concentration can greatly reduce  $^{48}\text{V}$  elution from Sep-Pak QMA(1).

Vanadium release varies strongly with carbonate concentration. Lower carbonate concentrations lead to greater vanadium sequestration on the QMA Sep-Pak, for a given level of  $^{18}\text{F}$  recovery.

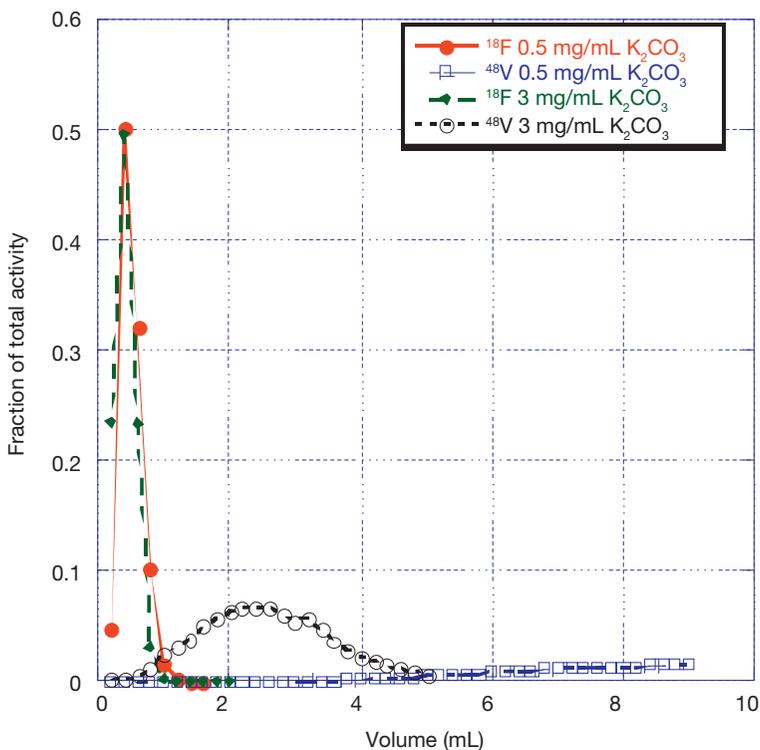


FIG. 4.3. Fluorine-18 and  $^{48}\text{V}$  elution profiles for two concentrations of aqueous carbonate.

#### 4.2. CONTAMINANTS IN THE PRECURSOR $^{18}\text{F}$

As has been mentioned, [ $^{18}\text{F}$ ]fluoride is usually produced in a metal target with a thin front window to admit the beam. The metal of choice for these windows is often Havar or titanium because of the high tensile strength and the chemical compatibility with the water and [ $^{18}\text{F}$ ]fluoride. Activation of the foil by the proton beam is unavoidable. Unwanted radioactive metal ions can leach into the target water and can conceivably enter the final radiotracer product. As mentioned in Section 4.1, the [ $^{18}\text{O}$ ] enriched water is often recovered using a quaternary ammonium ion exchange resin column to separate the [ $^{18}\text{F}$ ]fluoride from the [ $^{18}\text{O}$ ]water [4.13]. Metal ions can be observed coming off the resin column. A careful examination of the distribution of the radioactive species when using this resin recovery system has been carried out [4.20]. This can be compared with the list of radionuclides produced in the foil and target body, presented in Section 2.4.

Using a niobium target with a titanium foil, the long lived contaminants released from the target consisted of 2440 Bq of  $^{48}\text{V}$  and 0.6 Bq of  $^{46}\text{Sc}$ . The  $^{48}\text{V}$  was trapped on QMA(1) with more than 99% efficiency. The  $^{46}\text{Sc}$  was trapped with 28% efficiency. The scandium activity was not detected in the eluate of QMA(1). Vanadium activity eluted as shown in Fig. 4.3; 0.8 mL of 1 mg/mL  $\text{K}_2\text{CO}_3$  eluted 15 Bq of  $^{48}\text{V}$  from QMA(1). This was trapped with high efficiency (>98%) by QMA(2). Long lived contaminants were undetectable in any components other than the two QMA Sep-Paks. Thus, for a titanium window on the target, long lived contamination was effectively eliminated by the dual Sep-Pak method.

Using a niobium target with a Havar foil released over 6000 Bq of activity, consisting of 11 detected isotopes ( $^{51}\text{Cr}$ ,  $^{52}\text{Mn}$ ,  $^{54}\text{Mn}$ ,  $^{55}\text{Co}$ ,  $^{56}\text{Co}$ ,  $^{57}\text{Co}$ ,  $^{58}\text{Co}$ ,  $^{57}\text{Ni}$ ,  $^{93}\text{Mo}$ ,  $^{95\text{m}}\text{Tc}$  and  $^{96}\text{Tc}$ ). A total of 3000 Bq were trapped on QMA(1), of which approximately 500 Bq eluted with the carbonate. This was primarily manganese, cobalt and technetium.

Using a titanium target body with a Havar foil, ten radioisotopes are detected in the recovered water (2 mL). The activities of these radioisotopes are shown in Table 4.1. The gamma ray spectrum of recovered water is shown in Fig. 4.4.

Figure 4.5 and Table 4.2 show the activities of different radioisotopes measured in the QMA cartridge. From Tables 4.1 and 4.2, it can be concluded that QMA retained 25–90% of activity, depending on the radioisotope.

TABLE 4.1. ACTIVITIES OF THE RADIONUCLIDES DETECTED IN RECOVERED WATER

Isotope	$T_{1/2}$ (h)	$E$ (KeV)	Gamma (%)	Activity (Bq/2 mL)
$^{57}\text{Co}$	6522.48	122.06	85.6	20.8
$^{51}\text{Cr}$	664.87	320.08	9.8	83.4
$^{95}\text{Tc}$	20	765.64	94.3	12.1
$^{96}\text{Tc}$	104.4	778.1	100	3.4
$^{58}\text{Co}$	1698.72	810.67	99.4	220.9
$^{54}\text{Mn}$	7488	835	99.9	0.4
$^{56}\text{Co}$	1850.88	846.7	99.92	54.7
$^{55}\text{Co}$	17.54	931.2	75	180
$^{48}\text{V}$	383.4	983.4	100	0.8
$^{52}\text{Mn}$	136.8	1433.9	100	17.0

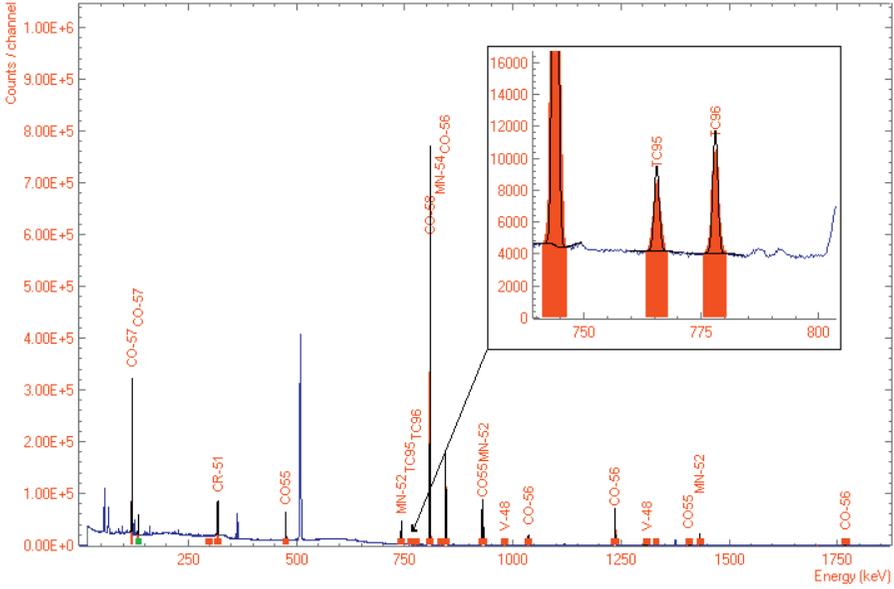


FIG. 4.4. Gamma spectrum of recovered water; the low activities of  $^{95}\text{Tc}$  and  $^{96}\text{Tc}$  are shown in the separate spectrum.

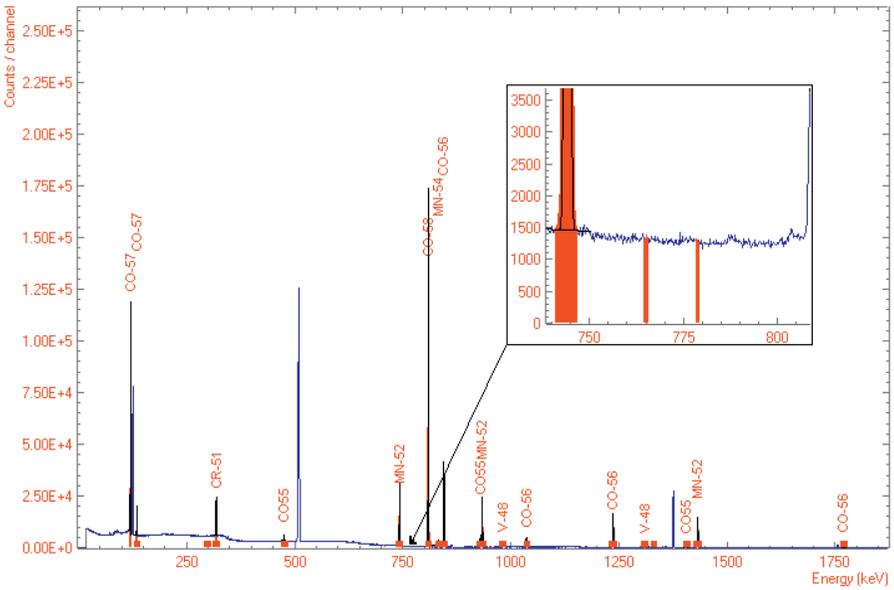


FIG. 4.5. Gamma spectrum of the QMA cartridge.

TABLE 4.2. ACTIVITIES OF THE RADIONUCLIDES MEASURED IN THE QMA CARTRIDGE

Isotope	$T_{1/2}$ (h)	$E$ (KeV)	Gamma (%)	Activity (Bq)
$^{57}\text{Co}$	6522.5	122.1	85.7	9.1
$^{51}\text{Cr}$	664.9	320.1	9.9	28.1
$^{95}\text{Tc}$	20	765.6	94.3	0.0
$^{96}\text{Tc}$	104.4	778.1	100	0.0
$^{58}\text{Co}$	1698.7	810.7	99.5	59.8
$^{54}\text{Mn}$	7488	835.1	99.9	0.9
$^{56}\text{Co}$	1850.9	846.7	99.9	15.5
$^{55}\text{Co}$	17.5	931.2	75	52.2
$^{48}\text{V}$	383.4	983.4	100	0.3
$^{52}\text{Mn}$	136.8	1433.9	100	16.3

#### 4.3. REUSE OF $^{18}\text{O}$ WATER

Efficient methods for the recovery of enriched isotopes from targets need to be developed, particularly the reuse of  $^{18}\text{O}$  enriched water for the production of FDG. In the future, targets capable of withstanding higher beam currents may require larger volumes of water to be used in each target load. Although the price of enriched water is lower than it has been in the past, and the supply seems to be much more stable now than it was a few years ago, the need for enriched water is increasing rapidly with the opening of many new centres for the production of FDG for clinical use. The question arises that if recycled water were to be used for patients, would the quality of the FDG be the same as it is with fresh water? In order to make it completely safe for repeated use, the water must be purified and be of the same quality that it was when it came from the manufacturer. In order to ensure that this is the case, several steps must be taken. It is necessary to completely characterize the water in terms of the isotopic purity, the chemical purity and the biological purity, in order to satisfy the requirements of good manufacturing practices (GMP). In other words, it must be of known enrichment, not have any chemical or radionuclide impurities, and be sterile and pyrogen free. When the manufacturer supplies the water, it is accompanied by a certificate of analysis, and if the water is to be recycled, it must come with the same assurances.

Impurities in irradiated [ $^{18}\text{O}$ ] water can be grouped as organic, ionic and radionuclidic. If they are not removed from the water, these impurities can cause pressure to build up in the cyclotron target, decrease the chemically reactive [ $^{18}\text{F}$ ]fluoride yield and/or decrease the [ $^{18}\text{F}$ ]FDG yield when it is re-irradiated.

Organic impurities that may come from the synthesis module for [ $^{18}\text{F}$ ]FDG are acetonitrile, acetone and ethanol [4.21]. Ionic impurities are anions such as  $\text{Br}^-$ ,  $\text{Cl}^-$ ,  $\text{F}^-$ ,  $\text{NO}_3^-$ ,  $\text{SO}_4^{2-}$ ,  $\text{PO}_4^{3-}$  or cations such as  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Fe}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$  and  $\text{NH}_4^+$ .

It is reported in the literature that some radioisotopes are also produced due to activation of the target body and target foil. Production of these radioisotopes depends on the energy of the protons, the beam current and the target material. Isotopes of cadmium, cobalt, iron, nickel, manganese and technetium were identified when a silver target was used. With a titanium target,  $^{48}\text{V}$  was observed. No radionuclides were detected in the final [ $^{18}\text{F}$ ]FDG product [4.22–4.25].

The beta emitting radionuclide  $^3\text{H}$  is also believed to be produced by the  $^{18}\text{O}(\text{p,t})^{16}\text{O}$  reaction in the target. Tritium was detected in the irradiated [ $^{18}\text{O}$ ]H $_2$ O, but it was not detected in purified [ $^{18}\text{F}$ ]FDG solution [4.26].

Various methods, such as ozonation [4.27], ultraviolet (UV) irradiation and He purge [4.28], potassium permanganate treatment, and electrolysis [4.29], have been reported for removing organic materials in irradiated [ $^{18}\text{O}$ ]H $_2$ O. Distillation followed all of these methods to remove organic impurities and oxidation by-products completely [4.29]. The distillation method is easy and practical but material losses occur. It is not useful for azeotropic mixtures either [4.27]. Therefore, it is more suitable to apply distillation after UV irradiation, electrolysis, gas purge (He) or ozonation.

An inert gas purge, such as with He, can remove organic compounds, but it does not completely remove organic impurities with a high boiling point [4.28]. Organic impurities can be removed by electrolysis, but this requires a special hydrolysis cell [4.28]. UV irradiation and ozonation can remove organic impurities by oxidizing them. These methods produce hydroxyl radicals, which oxidize organic impurities and form  $\text{CO}_2$  and water [4.27]. The solid phase extraction (SPE) method also has limited use for removing ionic impurities [4.28].

There are two important concerns for using irradiated [ $^{18}\text{O}$ ]water. First, purified water must be as chemically pure as fresh [ $^{18}\text{O}$ ]water and free from radionuclides, which make their way into the final product. Chemical impurities must be removed using the techniques mentioned previously, to the extent possible. Second is the isotopic enrichment of  $^{18}\text{O}$ . During [ $^{18}\text{F}$ ]FDG synthesis, enrichment of the  $^{18}\text{O}$  water is reduced because of the solutions that are used for synthesis and oxidation processes. The lower enrichment of the water will result in a decrease in the  $^{18}\text{F}$  yield. To determine  $^{18}\text{O}$  enrichment, the simple gravimetric method given by Fawdry [4.30] can be used. The [ $^{18}\text{F}$ ]FDG percentage production yields using purified [ $^{18}\text{O}$ ]H $_2$ O are comparable to those with fresh [ $^{18}\text{O}$ ]H $_2$ O.

#### 4.4. TRANSPORT OF $^{18}\text{F}$ TO THE HOT CELL

Transport of the water containing the  $^{18}\text{F}$  is usually carried out using small bore plastic tubing. The most common materials for this tubing are polyethylethylketone or polyethylene. Both these materials are very low in fluorine, so they should not be detrimental to the SA of the  $^{18}\text{F}$ . There are reports from different laboratories that the transfer of water through this line often has associated problems with a delay in the return of the activity or, as a worst case, no delivery at all.

In any small bore tubing transporting a liquid with gas pressure, there are several possible modes of transport, depending on the ratio of gas to water and on the surface tension of the liquid with respect to the walls of the tubing. Since water has a very high surface tension, it can cause problems with the transfer of the liquid, resulting in a low percentage of the liquid actually making it to the end of the line. The possible arrangements and the names given to these arrangements are shown in Fig. 4.6.

In practice, the water is broken up as shown in Fig. 4.7, which most closely resembles the plug flow model of transport.

As the liquid breaks up into more sections, each section contributes to the surface tension that must be overcome to push the liquid through the tube (Fig. 4.8). If the pressure is increased to overcome this resistance, there is a greater tendency

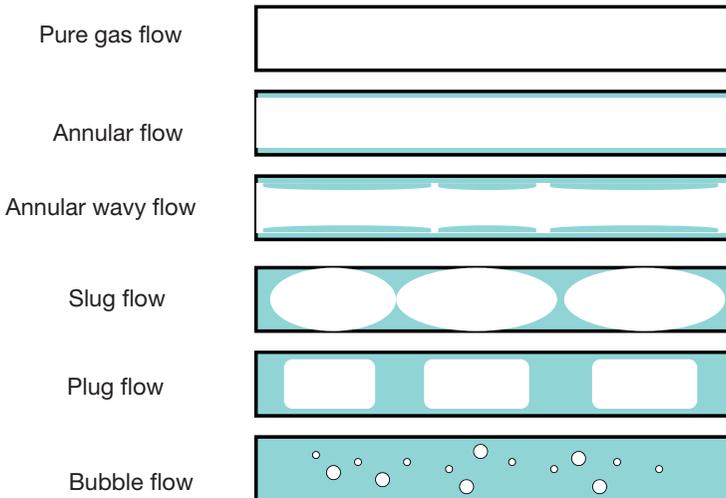


FIG. 4.6. Models of water transport in a plastic line.



FIG. 4.7. Picture of the water broken up into several sections in the plastic tubing.

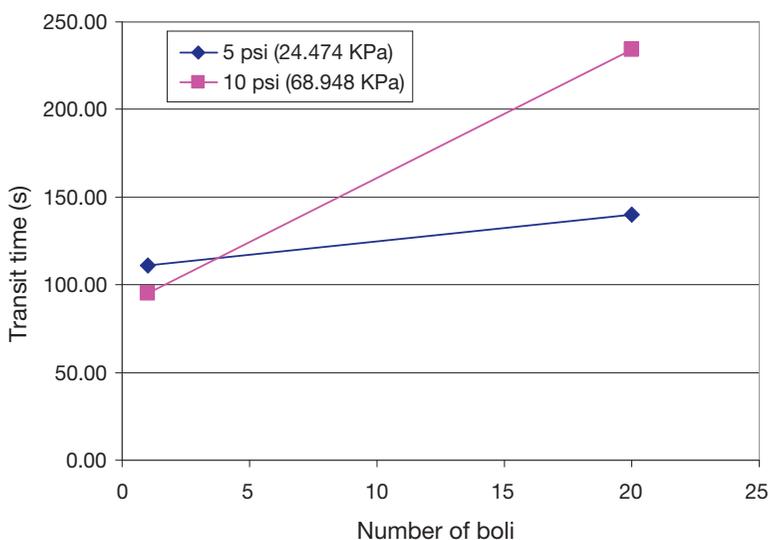


FIG. 4.8. Transit time for water through microline tubing (polyethylene) broken into different numbers of sections (boli) and at different push gas pressures.

for the liquid to break up, until eventually the liquid is all residing on the sides of the tubing and the gas is passing through the centre, decreasing the apparent yield of the target. This is shown in Fig. 4.6 as annular or annular wavy flow.

In order to reduce the probability of this happening, it is important to keep the lines clean, to reduce the amount of surface tension between the water and the tube wall. This can be done by rinsing through with an organic solvent or by rinsing with pure deionized water from time to time, to remove any residue of salt deposited by the carbonate solution, usually used to elute the  $^{18}\text{F}$  from the QMA cartridge.

#### 4.5. SA CONSIDERATIONS

The SA of both  $^{11}\text{C}$  and  $^{18}\text{F}$  labelled precursors produced in the target will determine the ultimate limit for the SA of the radiolabelled tracers produced through the labelling chemistry. At present, little is known about the performance with regard to the SA of the commonly used commercially available target systems. In most cases, knowledge about SA is derived from analysis of the radiolabelled end products. It is noteworthy that for both  $^{11}\text{C}$  and  $^{18}\text{F}$  labelled tracers, the values measured are quite far from the theoretical maximum values (9200 and 1730 Ci/ $\mu\text{mol}$ , respectively, 341 versus 63.4 TBq/ $\mu\text{mol}$ ). At present, typical values for SA for the tracers are in the range of 1–20 Ci/ $\mu\text{mol}$  at the end of synthesis. The reasons for the failure to even come close to the theoretical values are at present undetermined. In order to elucidate the role of carrier introduction to the system as a whole, it is necessary to differentiate between the radionuclide production in the target and the further manipulation of the radionuclide. Possible sources of introduction of stable material include air components (especially  $\text{CO}_2$ ) and various materials used in target handling components, such as packing materials in valves, tubing materials, etc., as well as the target chamber materials themselves.

The carrier fluoride in the water target used for the production of [ $^{18}\text{F}$ ]fluoride is a case in point. Here, the SA is often limited by the amount of carrier fluoride in the  $^{18}\text{O}$  enriched water used. It has been shown that the amount of fluoride does not increase on prolonged irradiation, as can be the case with  $^{11}\text{C}$ . This suggests that the target body material is not a source of fluoride. Carrier fluoride can be added through the water handling system, since the valves used in most of these systems contain polymeric O-rings or gaskets that are manufactured with fluorine in some form or another. This makes it very difficult to obtain very high SA [ $^{18}\text{F}$ ]fluoride without extreme care in the choice of materials used in the handling system. Some common materials and the amount of covalently bound fluorine contained in each are given in Table 4.3.

TABLE 4.3. FLUORINE IN COMMON MATERIALS

Material	Fluorine (weight %)
Teflon (polytetrafluoroethylene, PTFE)	76
Kel-F	49
Needle valve packing material	50
Viton	0.002
Polyethylene	N.D. <sup>a</sup> (<0.0004%)

<sup>a</sup> N.D.: not detectable.

There is a clear need to reach reliable production of high SA radiopharmaceuticals, as present-day tracers and certainly future tracers include receptor/transporter ligands that are highly toxic. As PET should be a true tracer technique, receptor occupancy with the radiolabelled tracer should be kept below about 1%, in order to avoid pharmacological/toxic effects. For the most commonly used PET radiopharmaceutical [ $^{18}\text{F}$ ]FDG, the SA is not a problem.

High SA for the typical  $^{11}\text{C}$  and  $^{18}\text{F}$  products, [ $^{11}\text{C}$ ]CH<sub>4</sub>, [ $^{11}\text{C}$ ]CO<sub>2</sub> and [ $^{18}\text{F}$ ]F<sup>-</sup> (aq), places a challenge for various radioanalytical techniques. Methods used are typically chromatographic, including GC and HPLC. Various sensitive and selective mass detectors are used, the gold standard today being mass spectroscopic systems. Ion liquid chromatography is a preferred method for the analysis of fluoride anions, although the sensitivity is somewhat limited. For [ $^{11}\text{C}$ ]CH<sub>4</sub>, GC/FID (flame ionization detection) is highly sensitive.

There is a clear need for simple standardized tests for the common precursors, where the sensitivity for analysis from a small aliquot from the production batch should be in the region of 100 Ci (3.7 GBq)/ $\mu\text{mol}$ .

With very potent and/or toxic substances, the reliable production of high SA radiopharmaceuticals is of paramount importance. The utility of radio-HPLC with UV-absorbance detection is limited in analyses of preparations with high SA. In most cases, the sensitivity is not high enough. The high sensitivity of liquid chromatography–mass spectrometry (LC–MS) makes it possible to measure masses accurately in the picogram range. The maximum specific radioactivity ( $\text{SA}_{\text{max}}$ ) will be higher for radioisotopes with shorter half-lives. The  $\text{SA}_{\text{max}}$  for  $^{18}\text{F}$  is 63.4 TBq/ $\mu\text{mol}$ , which is seldom approached in  $^{18}\text{F}$ -labelling chemistry. A SA of the order of 100 GBq/ $\mu\text{mol}$  at the end of synthesis is generally considered high. In this range or lower, the SA will decline essentially with the half-life of  $^{18}\text{F}$ . If, however, the SA approaches the theoretical value, the initial decline of SA as a function of time will be slower and will be in proportion to the initial ratio of  $^{19}\text{F}$  to  $^{18}\text{F}$  labelled substance.

In theory, due to shorter half-life, the maximum SA for  $^{11}\text{C}$  is higher than for  $^{18}\text{F}$  (341 versus 63.4 TBq/ $\mu\text{mol}$ , respectively). In practice, it turns out to be quite difficult to prepare  $^{11}\text{C}$  methylation agents with a SA greater than 700 GBq/ $\mu\text{mol}$ , whereas careful exclusion of carrier fluoride in  $^{18}\text{F}$  production systems can give a SA in excess of 4 TBq/ $\mu\text{mol}$ . This difference is accentuated by the fact that SA will decline with the half-life of the radioisotope.

The  $\text{SA}_{\text{max}}$  is a function of the radionuclide half-life only and will not change with time if no part of the preparation is a compound containing the stable isotope:

$$\text{SA}_{\text{max}} = N_{\text{A}} \times \ln 2 / T_{1/2} \quad (7)$$

This is not the case in most PET radiochemistry. The amount of the unlabelled compound will by far exceed the labelled product. The SA of the product will, therefore, exponentially decline with the half-life of the radioisotope:

$$SA(t) = \frac{A(t)e^{(-\ln 2t/T_{1/2})}}{m} \quad (8)$$

where

$A$  is the amount of radioactivity (Bq);

$t$  is the time (s);

$T_{1/2}$  is the half-life of the isotope in question;

and  $m$  is the mass (mol).

#### 4.6. TECHNIQUES FOR MEASURING FLUORINE MASS

Ion chromatography and ion specific electrodes are good examples of methods being used to measure fluoride concentrations. LC-MS may also be used. However, one needs to understand the limitations of these methods. Ion chromatography is the gold standard for measuring fluoride concentration. It tends to be tedious and labour intensive to keep up and running. Most people do not systematically follow the fluoride content of their aqueous [ $^{18}\text{F}$ ]fluoride solutions, but rather follow the specific activities of the radiotracers prepared with this fluoride using HPLC methods. Using LC-MS/MS is also an excellent method to determine the SA of the final radiotracer if the resource is available.

#### REFERENCES TO SECTION 4

- [4.1] KILBOURN, M., Fluorine-18 Labeling of Radiopharmaceuticals, National Academy Press, Washington, D.C. (1990).
- [4.2] RUTH, T., WOLF, A.P., Absolute cross section for the production of  $^{18}\text{F}$  via the  $^{18}\text{O}(p,n)^{18}\text{F}$  reaction, Radiochim. Acta **26** (1979) 21.
- [4.3] CASELLA, V., et al., Anhydrous  $^{18}\text{F}$  labelled elemental fluorine for radiopharmaceutical production, J. Nucl. Med. **21** (1980) 750.
- [4.4] NICKLES, R., DAUBE, M., RUTH, T., An  $\text{O}_2$  target for the production of [ $^{18}\text{F}$ ]F $_2$ , Appl. Radiat. Isotopes **35** (1984) 117.
- [4.5] SOLIN, O., BERGMAN, J., Production of  $^{18}\text{F}$ -F $_2$  from  $^{18}\text{O}_2$ , J. Labelled Compd. Rad. **23** (1986) 1202.

- [4.6] CACACE, F., SPERANZA, M., WOLF, A., FOWLER, J., Labelling of fluorinated aromatics by isotopic exchange with [<sup>18</sup>F]fluoride, *J. Labelled Compd. Rad.* **18** (1981) 1721.
- [4.7] WATKINS, G., TOORONIGAN, S., MULHOLLAND, G., Facile production of anhydrous F-18 hydrogen fluoride during committed deuteron bombardment schedules, *J. Nucl. Med.* **28** (1987) 1082.
- [4.8] NICKLES, R., et al., An <sup>18</sup>O<sub>2</sub> target for the high yield production of <sup>18</sup>F-fluoride, *Appl. Radiat. Isotopes* **34** (1983) 625.
- [4.9] NICKLES, R., GATLEY, S.J., VOTAW, J., KORNGUTH, M., Production of reactive fluorine-18, *Appl. Radiat. Isotopes* **37** (1986) 649.
- [4.10] ALEXOFF, D., SCHLYER D., WOLF, A.P., Recovery of [<sup>18</sup>F]fluoride from [<sup>18</sup>O]water in an electrochemical cell, *Appl. Radiat. Isotopes* **40** (1989) 1.
- [4.11] SCHLYER, D., BASTOS, M., WOLF, A.P., A rapid quantitative separation of fluorine-18 fluoride from oxygen-18 water, *J. Nucl. Med.* **28** (1987) 764.
- [4.12] JEWETT, D., et al., Multiphase extraction: Rapid phase transfer of [<sup>18</sup>F]fluoride for nucleophilic radiolabeling reactions, *Appl. Radiat. Isotopes* **39** (1988) 1109.
- [4.13] SCHLYER, D., BASTOS, M., ALEXOFF, D., WOLF, A.P., Separation of [<sup>18</sup>F]fluoride from [<sup>18</sup>O]water using anion exchange resin, *Appl. Radiat. Isotopes* **41** (1990) 531.
- [4.14] MULHOLLAND, S., TOORONGIAN, G., JEWETT, D., KILBOURN, M., Polymer supported NCA nucleophilic radiofluorination: rapid new synthesis of [<sup>18</sup>F]FDG with recovery of [<sup>18</sup>]water, *J. Nucl. Med.* **29** (1988) 754.
- [4.15] MULHOLLAND, G., MANGER, T., JEWETT, D., KILBOURN, M., Polymer supported nucleophilic radiolabeling reactions with [<sup>18</sup>F]fluoride and [<sup>11</sup>C]cyanide ion on quaternary ammonium resins, *J. Labelled Compd. Rad.* **26** (1989) 378.
- [4.16] HAMACHER, K., COENEN, H., STOCKLIN, G., Efficient stereospecific synthesis of no-carrier-added 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution, *J. Nucl. Med.* **27** (1986) 235.
- [4.17] KIESEWETTER, D., et al., Syntheses and D<sub>2</sub> receptor affinities of derivatives of spiperone containing aliphatic halogens, *Appl. Radiat. Isotopes* **37** (1986) 1181.
- [4.18] TEWSON, T.J., Procedures, pitfalls and solutions in the production of [<sup>18</sup>F]2-deoxy-2-fluoro-D-glucose: a paradigm in the routine synthesis of fluorine-18 radiopharmaceuticals, *Nucl. Med. Biol.* **16** (1989) 533.
- [4.19] HAMACHER, K., BLESSING, G., NEBELING, B., Computer aided synthesis of no-carrier-added 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic fluorination., *Appl. Radiat. Isotopes* **41** (1990) 49.
- [4.20] SCHUELLER, M.J., ALEXOFF, D.L., SCHLYER, D.J., Separating long-lived metal ions from <sup>18</sup>F during H<sub>2</sub><sup>18</sup>O recovery, *Nucl. Instrum. Meth. B* **261** 1–2 (2007) 795–799.
- [4.21] KITANO, H., MAGATA, Y., TANAKA, A., MUKAI, T., Performance assessment of O-18 water purifier, *Ann. Nucl. Med.* **15** 1 (2001) 75–78.
- [4.22] GILLIES, J.M., NAJIM, N., ZWEIT, J., Analysis of metal radioisotope impurities generated in [<sup>18</sup>O]H<sub>2</sub>O during the cyclotron production of fluorine-18, *Appl. Radiat. Isotopes* **64** (2006) 431–434.
- [4.23] ITO, S., SAKANE, H., DEJI, S., SAZE, T., NISHIZAWA, K., Radioactive byproducts in [<sup>18</sup>O]H<sub>2</sub>O used to produce <sup>18</sup>F for [<sup>18</sup>F]FDG synthesis, *Appl. Radiat. Isotopes* **64** (2006) 298–305.

- [4.24] MARENGO, M., et al., Assessment of radionuclidic impurities in 2- $^{18}\text{F}$ fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ FDG) routine production, *Appl. Radiat. Isotopes* **66** (2008) 295–302.
- [4.25] WILSON, J.S., AVILA-RODRIGUEZ, M.A., JOHNSON, R.R., ZYUZIN, A., MCQUARRIE, S.A., Niobium sputtered Havar foils for the high-power production of reactive  $^{18}\text{F}$ fluoride by proton irradiation of  $^{18}\text{O}$ H<sub>2</sub>O targets, *Appl. Radiat. Isotopes* **66** (2008) 565–570.
- [4.26] ITO, S., et al., Tritium in  $^{18}\text{O}$  water containing  $^{18}\text{F}$  fluoride for  $^{18}\text{F}$ FDG synthesis, *Appl. Radiat. Isotopes* **61** (2004) 1179–1183.
- [4.27] ASTI, M., et al., Purification by ozonolysis of  $^{18}\text{O}$  enriched water after cyclotron and the utilization of the purified water for the production of  $^{18}\text{F}$ -FDG (2-deoxy-2- $^{18}\text{F}$ fluoro-D-glucose), *Appl. Radiat. Isotopes* **65** (2007) 831–835.
- [4.28] MOON, W.Y., et al., Simple purification of recovered  $^{18}\text{O}$ H<sub>2</sub>O by UV, ozone, and solid-phase extraction methods, *Appl. Radiat. Isotopes* **65** (2007) 635–640.
- [4.29] HUANG, B., CHANNING, M., PLASCJAK, P., KIESEWETTER, D., Routine quality control of recycled target  $^{18}\text{O}$ water by capillary electrophoresis and gas chromatography, *Nucl. Med. Biol.* **30** (2003) 785–790.
- [4.30] FAWDRY, R.M., A simple effective method for estimating the  $^{18}\text{O}$  enrichment of water mixtures, *Appl. Radiat. Isotopes* **60** (2004) 23–26.

## 5. GAS TARGETS — OPERATIONAL CONSIDERATIONS

### 5.1. PRESSURE VERSUS CURRENT — DENSITY REDUCTION EFFECTS

A major concern in target design is the generation and dissipation of heat during irradiation. Efficient cooling not only ensures that the target material will remain in the target, but also allows the target to be irradiated at higher beam currents, which in turn allows production of more radioisotopes in a given time. As the target gas gets hotter, the density of the gas decreases. This phenomenon of density reduction has been studied extensively, and there are some simple tests that can be done to see if density reduction is a problem with a particular gas target [5.1].

In small volume targets, this problem is more serious. The small size means that these targets must be run at high pressure, where foil rupture is a distinct possibility. In a typical gas target, the total length is of the order of 10–15 cm. In order to produce  $^{11}\text{C}$ , the target must be operated at about 20 atmospheres (2.0265 MPa). Since the volume is small, the pressure rise is large. The pressure rise is correlated with the temperature rise in the target and the target comes to equilibrium fairly quickly. There have been several attempts to predict the density reduction in the target from the observable parameters such as pressure. The first relationship was given by Lambrecht [5.2] (Fig. 5.1) as:

$$\frac{P_1}{P_0} = aI^b \quad (9)$$

where

$P_1$  is pressure;

$P_0$  is original pressure;

and  $I$  is beam current.

It has also been noted that the ratio of pressure rise reaches a maximum when there is just enough gas in the target to stop the beam. As the pressure increases, the ratio falls as the heat transfer is improved. The pressure required to stop the beam is dependent on both the energy and the beam current, and the variable is the total power deposited in the gas by the beam. It has also been noted that convective flow patterns are set up in the target, which move the heat from the central region to the vicinity of the target walls. This temperature variation inside the target accounts for some fraction of the apparent density reduction. Other factors are also important, such as small angle multiple scattering and energy straggling. These factors can be easily calculated and factored out, leaving only the thermal gradients [5.3].

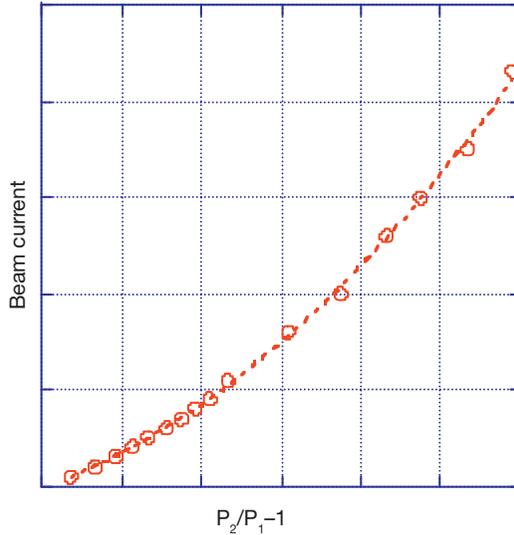


FIG. 5.1. Plot of typical pressure ratio (beam on/beam off) versus beam current for a gas target.

## 5.2. INTERNAL CIRCULATION AND HEAT REMOVAL

In order to have a useful accelerator target for the production of a radionuclide, it is necessary to effectively remove the heat generated by the beam. The three modes of heat transfer that are active in gas targets are conduction, convection and radiation. Radiation is only significant at high temperatures (>500°C). Gases and liquids usually transfer heat via convection and conduction. Heat transfer in solids is somewhat simpler than in other media, since the heat usually flows through the target matrix, mainly by conduction.

Once the heat has been transferred from the gas or liquid to the target body, it will usually be removed by water flowing around the target. Most heat transfer problems arise in the interfaces, where there are discontinuities in the heat transfer, such as where the target material meets the target body or where the target body meets the cooling water. The more efficient the design of the transfer at these interfaces, the better the heat transfer will be and the less likely it is that there will be problems with loss of target material or damage to the target during the irradiation.

When considering heat transfer in cyclotron targets, both free convection and forced convection come into play. In either gas or liquid targets, the fluid inside the target is heated to high temperatures, usually with a non-uniform distribution of the heating. The result of this uneven distribution of heating will

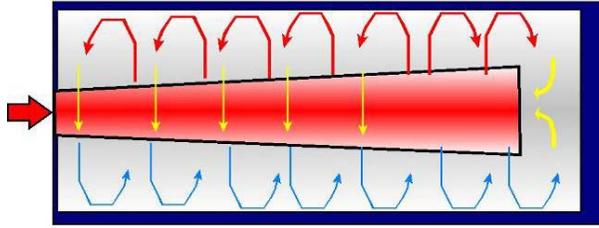


FIG. 5.2. Schematic diagram of the flow circulation patterns set up inside the gas target (from Ref. [5.3]).

result in convection currents being set up inside the target. These free convection currents are useful in helping remove the heat from the fluid and decreasing the effects of density reduction. Forced convection of water around the outside of the target body is often used to remove the heat transferred to the target body by the internal convection of the target fluid. The front foils on targets are also often cooled with a forced stream of some inert gas such as helium. Helium is particularly useful because of its low viscosity and because it does not become activated in the proton beam.

### 5.2.1. Internal circulation

Figure 5.2 shows how the convection currents might be set up in a static target during irradiation [5.3]. If the gas is flowing through the target, the situation is changed to one of forced convection, and the appropriate equations for this type of heat transfer can be used.

The heat transfer from the target gas to the target body occurs mainly at the interface. The mode of heat transfer has been studied, and it has been determined that the main mode is convection. The fraction of convection as a function of distance from the centre of the target is shown in Fig. 5.3 [5.4].

### 5.2.2. External target fins

One common way to increase the surface area for convective heat transfer is to use fins on the target (Fig. 5.4). Studies have been carried out to determine whether adding fins to the outside of the target body will help with heat transfer. In most cases, they do not significantly increase the efficiency of heat removal in this application. It is much more efficient to make the target body walls as thin as possible to hold pressure, since the convection from the target gas to the target body is usually the limiting factor in heat removal. This will depend on the material used and the thermal conductivity.

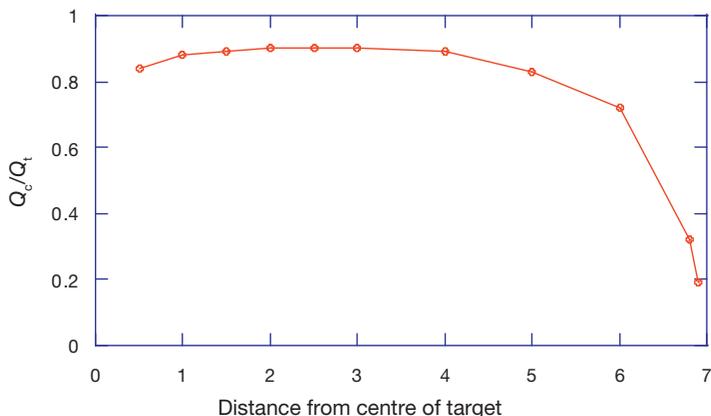


FIG. 5.3. Fraction of heat transferred by convection as a function of distance from the target centre.

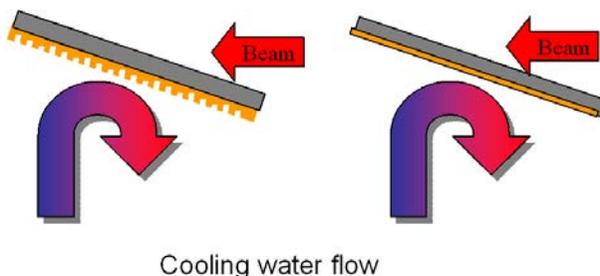


FIG. 5.4. Diagram of target body with and without fins.

The other factor in the use of fins is the type of flow the liquid will have. If the fins (or a rough surface) set up a turbulent flow, it will be much more effective in heat transfer than a laminar flow.

### 5.2.3. Internal target fins

In general, the fin helps to increase the heat transfer area from metal to fluid. A schematic diagram of this target is shown in Fig. 5.5, and the gas transfer system for this target is shown in Fig. 5.6.

The results from this target are shown in Fig. 5.7. The pressure rise in the target with the internal fins was  $200 \pm 20$  KPa at  $10 \mu\text{A}$ . This can be compared with the pressure rise in a target with the same length with no internal fins, which was about 400 KPa. The target with the internal fins also gave more stable production yields with longer irradiation time. The average yield was 92 mCi

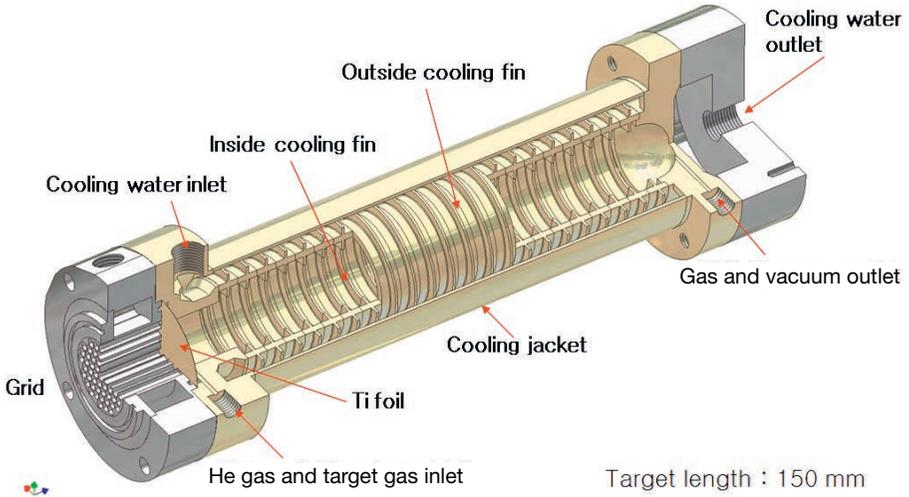


FIG. 5.5. New target design with cooling fin.

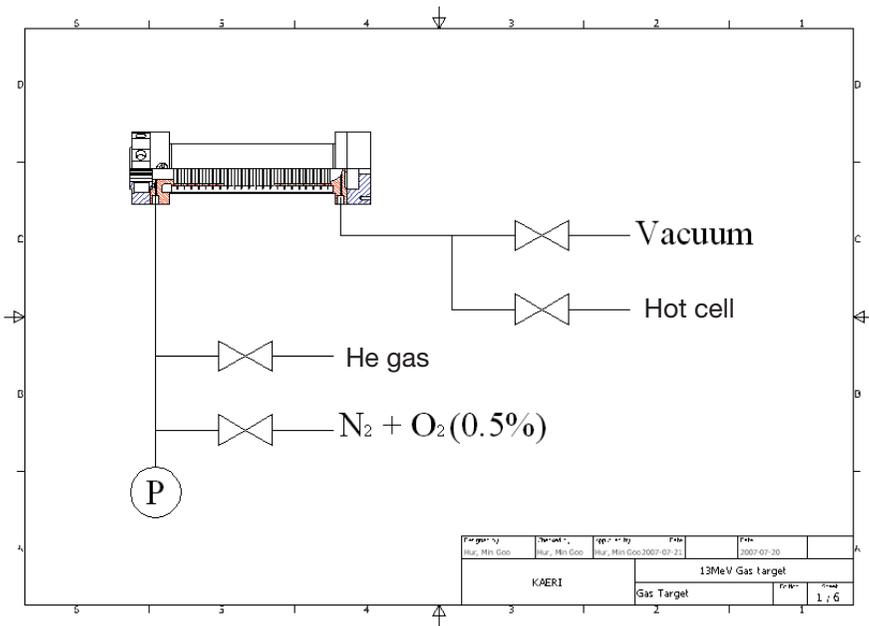


FIG. 5.6. Block diagram of targetry for  $^{11}\text{C}$  production with cooling fin.

(3.404 GBq)/ $\mu\text{A}$  at all times, compared with the yields in the target without internal fins, which dropped off at longer times.

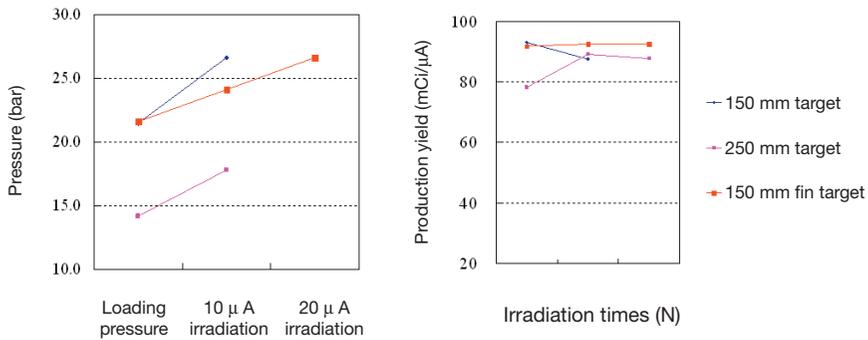


FIG. 5.7. Experimental results; 1 bar =  $10^5$  Pa.

This leads to several conclusions that need to be explored more fully. These are:

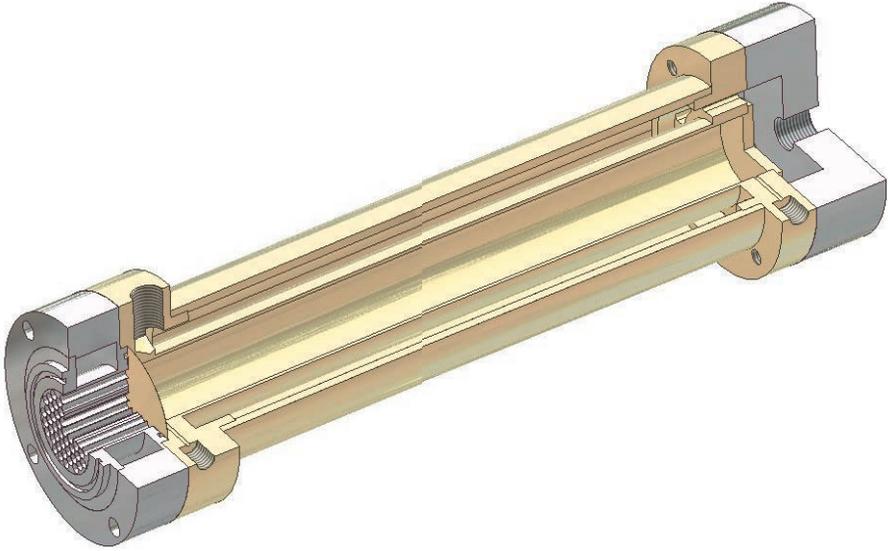
- Cooling fins inside the target can aid convective cooling of the target gas;
- Using cooling fins inside the target is effective in reducing the target pressure rise ratio, which indicates reduced density reduction effects;
- The radionuclide production yield with a target with internal fins was more stable for high current irradiation and at longer times;
- Based on these observations, the target with internal cooling fins may be a very useful design concept.

### 5.3. TARGET GEOMETRY (CONICAL VERSUS CYLINDRICAL, LENGTH)

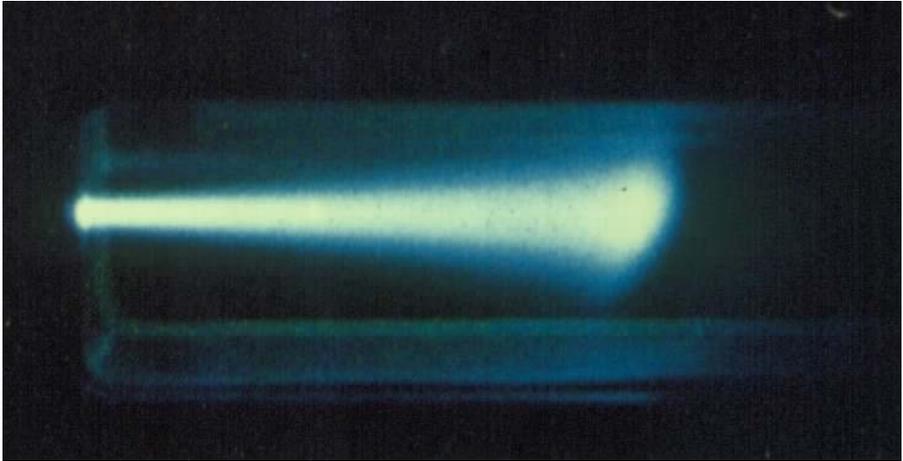
The basic geometries for gas targets are cylindrical and conical. The cylindrical type is the most common commercial design and the simplest structure to manufacture. It has a clean inner surface but can be damaged if the beam spreads into the wall, due to scattering in the foil or gas.

#### 5.3.1. Cylindrical targets

Figure 5.8 shows a cylindrical gas target for the production of  $^{11}\text{C}$ . The beam is incident through the front foil with a water cooled grid and the rear foil is cooled by heat transfer from a cooling water flow in the rear of the target. The rear foil is thin, to maximize the heat transfer. The inner capacity of the cylinder is 78.5 mL.



*FIG. 5.8. A cylindrical gas target for the production of  $^{11}\text{C}$ .*



*FIG. 5.9. Beam spreading due to scattering and beam heating effects in a gas target (from Ref. [5.3]).*

The beam typically spreads in gas targets due to multiple scattering and this effect is shown in Fig. 5.9.



FIG. 5.10. Conical design for  $^{11}\text{C}$  gas target.

### 5.3.2. Conical targets

Considering this beam characteristic, the conical type was developed. If the cone is shaped correctly, one can expect higher production yield and higher SA due to the lower total volume of the target as compared with a conical target with sufficient diameter to accommodate the beam scattering. A typical conical target design is shown in Fig. 5.10.

## 5.4. INNER SURFACE OF THE GAS TARGET

The inner surface of the aluminium gas targets is usually polished to a mirror finish. This surface usually remains as a shiny surface over years if there are no impurities irradiated in the target.

Niobium is a good chamber body material for in situ production of  $[^{11}\text{C}]\text{CH}_4$  using a target composed of 10%  $\text{H}_2/\text{N}_2$ . The production, as a function of time, can be represented by an empirically derived equation (Fig. 5.11) [5.5]. This

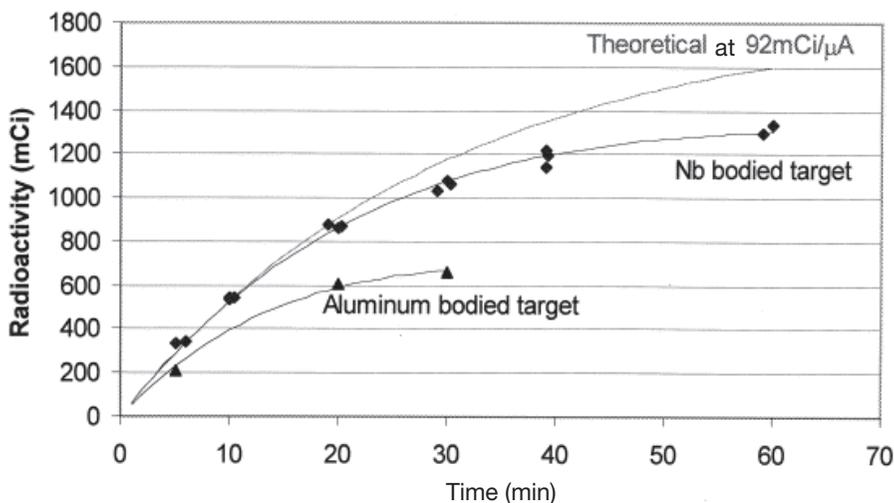


FIG. 5.11. Production of  $^{11}\text{C}$  as methane in different targets ( $1\text{ mCi} = 37\text{ MBq}$ ).

analysis elucidates the presence of a competing reaction limiting the formation of  $[^{11}\text{C}]\text{CH}_4$ .

The experimental data for our target systems can be fitted to a single exponential of the form:

$$Y = Ae^{-at}ISF \quad (10)$$

where

- $Y$  is the decay corrected yield (mCi);
- $A$  the fitted pre-exponential term (mCi/μA);
- $a$  is the fitted exponential term ( $\text{min}^{-1}$ );
- $I$  is the beam current (μA);
- $t$  is the length of irradiation (min);

and SF is the saturation correction factor ( $1 - e^{-\lambda t}$ ).

This is the standard yield equation, with the addition of a single exponential term to account for a first order reaction reducing the yield.  $A$  is equivalent to the saturation yield, while  $a$  represents a competing or leakage rate constant (Table 5.1).

TABLE 5.1. FITTED PARAMETERS  $A$  AND  $a$  FOR VARIOUS TARGET CHAMBER MATERIALS USED FOR IN SITU PRODUCTION OF  $[^{11}\text{C}]\text{CH}_4$

Target chamber	$A$	$a$ (10 000)
Niobium cylinder	$95 \pm 2$	$40 \pm 4$
Aluminium cone	$68 \pm 9$	$135 \pm 44$
Nickel cone	$65 \pm 9$	$527 \pm 67$
Stainless steel cylinder	$71 \pm 11$	$64 \pm 62$
Large aluminium cylinder	$70 \pm 9$	$180 \pm 52$

### REFERENCES TO SECTION 5

- [5.1] WIELAND, B.W., SCHLYER, D.J., RUTH, T.J., WOLF, A.P., Deuteron beam penetration in a neon gas-target for producing F-18, *J. Labelled Compd. Rad.* **18** (1981) 27–29.
- [5.2] WOJCIECHOWSKI, P.W., SAJJAD, M., LAMBRECHT, R.M., A semi-quantitative approach to the design, analysis and operation of a gas target system, *Appl. Radiat. Isotopes* **39** (1988) 429–436.
- [5.3] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Principles and Practice, Technical Reports Series No. 465, IAEA, Vienna (2009).
- [5.4] HUGEL, E.A., Investigations of the Production Environment of Carbon-11, Thesis No. AAT8907056, University of Michigan, Ann Arbor (1988).
- [5.5] BUCKLEY, K.R., JIVAN, S., RUTH, T.J., Improved yields for the in situ production of  $[^{11}\text{C}]\text{CH}_4$  using a niobium target chamber, *Nucl. Med. Biol.* **31** 6 (2004) 825–827.

## 6. GAS TARGETS — PRODUCT CONSIDERATIONS

### 6.1. PURITY OF TARGET COMPONENTS

One of the major concerns in PET is the SA of the  $^{11}\text{C}$ . Carbon can come from the walls of the target during irradiation, O-rings on the target, plastic lines going in and out of the target, or regulators used to supply the gas. The amount of carbon introduced by the target body during irradiation can be reduced by irradiating an inert gas mixture with oxygen in the target. If the target is kept leaktight and pressurized, the amount of carrier carbon should remain low. The quantity of activity recovered from the target is often reduced as the SA is increased. The yields can be increased by adding additional oxygen to the nitrogen gas. Metal O-rings (or C-rings) on the target are best for the elimination of contaminant carbon. There are several suppliers of these sealing systems. The plastic lines going in and out of the target should be kept to a minimum and only be long enough to allow electrical isolation, so that the beam current can be measured. It is often possible to run metal tubing inside plastic tubing and then seal the system on the plastic to avoid the target gas contacting plastic surfaces. Certainly, the plastics should not be too close to the target, to avoid radiation damage and degradation to the plastic. The regulators on the nitrogen gas handling systems should be of the high purity type. These are more expensive, but the extra cost will pay off in a higher SA for the  $^{11}\text{C}$ .

Another concern is the purity of the nitrogen gas used to fill the target. This should be of the highest quality obtainable. The gas can also be passed through a soda lime or other trap to remove any traces of carbon dioxide from the nitrogen. Care has to be taken, however, that the trap does not add carbon, which can happen if the absorbent material is saturated or is not well prepared prior to putting it in service.

### 6.2. TARGET STORAGE

There is some level of discussion as to whether the target should be left filled with gas or at atmospheric pressure. If the target is completely leaktight, there is no harm in leaving it at atmospheric pressure. However, tiny leaks can permit traces of carbon dioxide to creep into a target left at atmospheric pressure. An overpressure of nitrogen in the target will reduce (but not eliminate) entry of the tiny amounts of  $\text{CO}_2$  in the atmosphere into the target. Most people leave the target at atmospheric pressure when it is not in use.

### 6.3. GAS TARGET SA

One of the major difficulties of working with  $^{11}\text{C}$ , in addition to its short half-life, is the ability to achieve high enough SA. Due to the ubiquitous nature of  $^{12}\text{C}$  in the environment, it is very difficult to eliminate sources of carrier from the labelling reactions. Stable carbon is found in virtually all gases and reagents used in chemical reactions. Reagents such as lithium aluminium hydride are highly reactive toward carbon dioxide and immediately scavenge it from the air and solvents, making the synthesis of  $^{11}\text{C}$ -methyl iodide harder to achieve in high SA. However, even with this sea of carbon in the environment, PET chemists have been able to obtain SAs routinely in the range of 1–100 Ci (3.7 TBq)/ $\mu\text{mol}$ , as long as very careful procedures were followed. In fact, several receptor binding agents, such as raclopride and others, have been successfully prepared with SAs high enough for imaging of the dopamine receptor system [6.1].

#### 6.3.1. $^{11}\text{C}$ targets

Gas targets intended for the direct production of  $^{11}\text{CO}_2$  and  $^{11}\text{CH}_4$  both require strict attention to detail, to achieve consistent high SA of their respective products. For example, both targets were constructed as single foil, gridded, cylindrical 316 stainless steel targets with electropolished interior surfaces [6.2]. The 30 cm length was chosen to be 150% of the proton range at the operating 1.48 MPa (200 psig) nitrogen pressure. Gas enters from the rear and exits from the front, next to the 25  $\mu\text{m}$  Havar foil. Target gases ( $\text{N}_2 + 1\% \text{O}_2$ ;  $\text{N}_2 + 10\% \text{H}_2$ ) are all made from grade 6 constituents, and pass through acid cleaned stainless steel tubes. An extensive effort to pin down the sources of cold carbon made use of GC:

- $^{11}\text{CH}_4$ : Megabore MS-5A capillary column 150°C, 30 m; He; pulsed discharge detector.
- $^{11}\text{CH}_3\text{I}$ : Porapak Q 150°C, 1.8 m; He; electroconductivity detector.
- Finally, the finished methylated product (raclopride) with HPLC and UV absorption.

As many investigators have found, there are many contributors to the cold carbon load, but the detailed dependence on beam power and dwell times remains unclear.

In a systematic investigation of  $\text{N}_2$  (0.1%  $\text{O}_2$ ) for production of  $[^{11}\text{C}]\text{CO}_2$ , and  $\text{N}_2$  (5%  $\text{H}_2$ ) for production of  $[^{11}\text{C}]\text{CH}_4$ , the target performance of both targets in terms of saturation yields as a function of target body temperature and

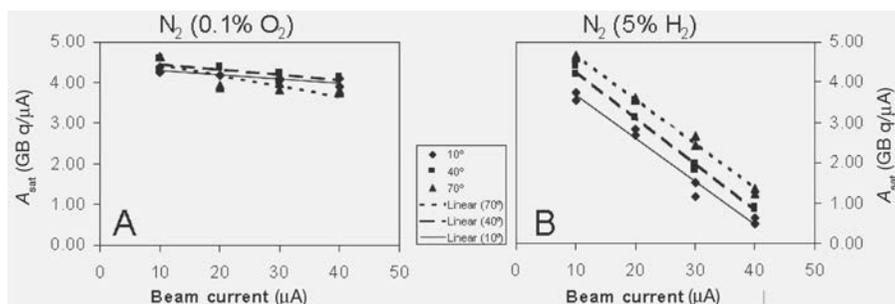


FIG. 6.1. Carbon-11 activity at saturation ( $A_{sat}$ ) from the nitrogen + oxygen target and the nitrogen + hydrogen targets as a function of temperature and beam current.

irradiation current were evaluated [6.2]. The results of this study are shown in Fig. 6.1.

Production of  $[^{11}\text{C}]\text{CO}_2$  is practically independent of the irradiation current and the target body temperature, whereas  $[^{11}\text{C}]\text{CH}_4$  production was found to be strongly dependent on the current and target body temperature.

### 6.3.2. $^{18}\text{F}_2$ gas targets

For the last three decades, electrophilic fluorination has commonly been carried out using the ‘two shoot’ technique [6.3]. A water cooled, 5052 aluminium target with a He cooled double foil entrance is first filled with pure  $^{18}\text{O}_2$  from a 1 mL cryoreservoir, half filled with Varian Microsorb. After irradiation, the enriched  $^{18}\text{O}_2$  gas is quantitatively recovered into the cryoreservoir. Less than 1% of the activity follows the gas, with the hundreds of millicuries of  $^{18}\text{F}$  remaining adsorbed on the target walls. The target is then pumped out and refilled with Kr containing 0.6%  $\text{F}_2$ . A second irradiation for 10–15 min forces the exchange of more than 50% of the activity into the gas phase, which is then bubbled out through the precursor dissolved in freon. Several points warrant attention. First, the krypton–fluorine mixture appears to quite stable, starting from a nominal 1% in 1990, to 0.8% in 1997, to about 0.6% in 2004, as shown by iodometry. Second, on several occasions a foil failure required replacement, with its associated exposure to room air between the first and second irradiations. The successful elution of active  $^{18}\text{F}_2$  appeared to be rather unaffected by this contact with room air. Finally, while the routine electrophilic syntheses are costly in terms of valve replacements, the actual procedure is remarkably reliable, with scant variation in radiochemistry yields.

#### 6.4. TECHNIQUES FOR MEASURING CARBON MASS

There are several reasons why  $^{11}\text{C}$  is an important radionuclide for use in tracer development. Two of the primary characteristics are that, with careful chemistry, the  $^{11}\text{C}$  can substitute for  $^{12}\text{C}$ , thus providing a molecule that is identical to one that is of interest in biological systems. The other is its short half-life, which means that the theoretical SA can be very high. Due to the ubiquitous nature of  $\text{CO}_2$ , it is difficult to eliminate all sources of carbon. Whatever the end product of the synthesis of the  $^{11}\text{C}$  containing molecule may be, there is usually a need to understand the SA. A number of studies have been undertaken over the years to determine the source of stable, bulk carbon and the techniques to measure it.

One of the best practical ways to measure carbon is in-line (with the target) GC with thermal conductivity detection (TCD), or FID or helium ionization detection (HID), and for SA radiation measurement in-line. In order to perform the measurement, the target has to be pumped out near to target with minimal fittings, so that the leaks do not cause a problem. Gas sampling valves have been shown to work well. TCD is relatively insensitive but radiation does not affect the response. However, both FID and HID can be affected by radiation, thus any radioactivity should be allowed to decay first before measurement. Alternatively, the response to radioactivity can be determined, to measure the effect on HID by counting pre- and post-decay (separate samples).

The second best method is as above but with the sample taken from a gas sampling container; however, there is a risk of contamination.

Obviously, multiple measurements should be conducted.

Another good method is the chemical indicator tube (such as the Kitigawa tube) but this takes an entire target load, and if the SA is too high it will not work (the sensitivity is not sufficient).

Finally, the amount of carrier carbon can be determined from secondary reactions. Performing secondary reactions is a good method, but one has to account for adding  $\text{CO}_2$  or methane, depending on the target yield in each step, so a direct use of  $\text{CO}_2$  is ultimately the best. One important aspect to remember is that Grignard reagents all have  $\text{CO}_2$  contamination.

$[^{11}\text{C}]$ hydrogen cyanide can be easily produced on-line from  $[^{11}\text{C}]$ cyanide by passing over platinum at  $1000^\circ\text{C}$  in the presence of ammonia. Since ammonia is produced in situ during irradiation of the  $[^{11}\text{C}]$ methane target by the radiolysis of nitrogen in the presence of hydrogen, this further simplifies the procedure. Cyanide can be quantified down to levels of parts per billion by HPLC using an electrochemical detector or by the use of colorimetric methods. After decay, the amount of cyanide can be measured using the pyridine–barbituric acid colorimetric test (König reaction, EPA method 335.4-1) [6.4] or other methods,

such as direct determination of free cyanide in drinking water by ion chromatography with pulsed amperometric detection [6.5], stable reagents for the colorimetric determination of cyanide by modified König reactions [6.6], and determination of total cyanide by semi-automated colorimetry [6.7].

Converting CO<sub>2</sub> to methane to cyanide in a closed system can be achieved with very little extra CO<sub>2</sub> added, and cyanide is very reactive. Phosgene adds carrier, and all of the gases add some methane, CO<sub>2</sub> and CO.

## 6.5. TRANSFER AND TRAPPING

When gas flows through a target while it is being irradiated with a charged particle beam, the pressure in the target is usually set with a regulator and the system remains at equilibrium. On the other hand, when the target is a closed system, the pressure in the target is significantly higher than the rest of the system and, therefore, when the pressure is released, there will be a gas flow along the pressure gradient to the low pressure end. If the volume of the system is high relative to the volume of the target, then a push gas is often required to increase the efficiency of the transfer. In either case, if the flow through the tube is laminar, the flow is governed by the Poiseuille equation.

$$F = \frac{\pi g r^4}{8 \mu L} \Delta P \quad (11)$$

where

$F$  is the flow in cm<sup>3</sup>/s;

$g$  is the gravitational acceleration (980.6 cm/s<sup>2</sup>);

$r$  is the radius of the tubing (cm);

$L$  is the length of the tubing (cm);

$\mu$  is the viscosity in poise (g·cm<sup>-1</sup>·s<sup>-1</sup>);

and  $\Delta P$  is the pressure differential (g/cm<sup>2</sup>).

To determine whether the Poiseuille equation is appropriate, it is necessary to determine whether the flow is laminar. This can be done using the Reynolds number.

This relation is:

$$\text{Re} = \rho V D / \mu \quad (12)$$

where

$Re$  is the Reynolds number (dimensionless);

$V$  is the flow velocity (cm/s);

$\rho$  is the density ( $\text{g}/\text{cm}^3$ );

$\mu$  is the viscosity in poise ( $\text{g}\cdot\text{cm}^{-1}\cdot\text{s}^{-1}$ );

and  $D$  is the tube diameter (cm).

If the Reynolds number is greater than about 2000, it means that the flow is turbulent and the Poiseuille equation is not valid. In this case, the flow will be somewhat slower than calculated using this equation. Flows of gases through a long tube, as is often the case in the lines connecting the chemistry labs to the cyclotron vault, is usually laminar. Some useful parameters for common fluids at 25°C are given in Table 6.1. These can be used in the flow equations to get approximate flow rates for gases or for water. Any bends or restrictions in the line, such as fittings or connections, will affect the flow of the gas through the line. The possibilities are too numerous to list here, but can be found in texts on mass transfer.

Since the production of  $^{11}\text{C}$  is usually performed in a gas target containing a large volume of nitrogen gas (with perhaps added oxygen), a simple maintenance free trapping technique has been developed to concentrate the  $[^{11}\text{C}]\text{CO}_2$  which, in turn, has made it possible to increase the yields of several radiotracers. It has the advantage of not using liquid nitrogen and having no moving parts other than the solenoid valves to contain the gas. Impurities coming from the target such as  $\text{O}_2$ ,  $\text{CO}$ ,  $\text{NO}$  and water are not retained on the trap and are, therefore, eliminated from further reactions which could interfere with the production or purity of the final product. The TE of 1 g of sieve is more than 99% for  $[^{11}\text{C}]\text{CO}_2$  coming from a 240 mL target and the release of the small bolus from the trap by thermal desorption is nearly quantitative.

TABLE 6.1. PARAMETERS FOR COMMON FLUIDS USED TO TRANSFER RADIOACTIVITY

Compound	Viscosity (centipoises)	Density ( $\text{g}/\text{cm}^3$ )
Air	0.0182	0.001185
Nitrogen	0.0176	0.00016
Helium	0.0196	0.001138
Water	0.890	1.0

Instead of using liquid nitrogen for  $[^{11}\text{C}]\text{CO}_2$  trapping, the cyclotron produced  $[^{11}\text{C}]\text{CO}_2$  is reversibly adsorbed to molecular sieves or Carbosphere material. After the controlled release, the  $[^{11}\text{C}]\text{CO}_2$  can be converted to other precursors such as  $[^{11}\text{C}]\text{methane}$  or  $[^{11}\text{C}]\text{cyanide}$ . The  $[^{11}\text{C}]\text{CH}_4$  generated is then absorbed and processed.

$[^{11}\text{C}]\text{methane}$  is quantitatively adsorbed from the target gas on a Porapak Q column cooled to the temperature of liquid nitrogen. Following absorptive concentration, the  $[^{11}\text{C}]\text{methane}$  is oxidized by passage over cobalt(II–III) oxide powder heated to  $500^\circ\text{C}$  in a stream of nitrogen–2.0% oxygen [6.8].

The results of the trapping experiments with the four trap designs described above show that increasing the length of the stainless steel tubing resulted in a concomitant increase in TE, with the 9 loop/4.8 m trap displaying a >99% TE at a flow rate of 500 standard cubic centimetres per minute (scm). Increasing the flow rate to 1000 scm resulted in a significant reduction (–10%) in TE with this design. This decrease in TE with respect to flow rate was not observed with either the stainless steel shot or frit assemblies at flow rates up to 1000 scm. The stainless steel wool assembly appeared to be 10–20% less efficient than the shot assembly at flow rates of 500 and 1000 scm, respectively. A bypass of the mass flow controller with the stainless steel frit trap in-line resulted in attainment of an initial flow rate that ranged from 2200 to 3500 scm, with a TE of 96%. Under these conditions, the trapped  $[^{11}\text{C}]\text{CO}_2$  was available for chemical manipulation by 3 min post-EOB. No significant difference in the rate of transfer of  $[^{11}\text{C}]\text{CO}_2$  from the trap to the soda lime cartridge upon removal of the liquid nitrogen and warming to room temperature was observed for the four trap designs (data not shown). The above data indicate that both the stainless steel shot and stainless steel frit assemblies may be suitable alternatives to the stainless steel or copper coiled tubing, or molecular sieve trapping systems that are in common use. Furthermore, the stainless steel frit assembly and requisite 100 mL Dewar/liquid nitrogen flask fits in a standard Capintec dose calibrator, which allows convenient quantitation of starting  $[^{11}\text{C}]\text{CO}_2$  activity for the chemical synthesis of  $^{11}\text{C}$  labelled radiopharmaceuticals. These two inexpensive, compact and highly efficient  $[^{11}\text{C}]\text{CO}_2$  trapping systems are of low volume and are fabricated entirely of stainless steel to allow for easy maintenance and cleaning in high SA remote chemistry systems. The reduced size of the trap means it is more readily shielded and requires minimal hot cell/fume hood space and may serve as an alternative method for trapping  $[^{11}\text{C}]\text{CO}_2$  of high SA [6.9].

## 6.6. WET VERSUS DRY CH<sub>3</sub>I TRIFLATE

[<sup>11</sup>C]methyl triflate has been proposed as a highly reactive alternative to [<sup>11</sup>C]methyl iodide. The reactivity of [<sup>11</sup>C]methyl iodide is, in most cases, sufficient for the routine production of PET radiopharmaceuticals. However, when considering PET radioligands where the yield from [<sup>11</sup>C]methyl iodide is relatively low, the use of [<sup>11</sup>C]methyl triflate may result in higher yields, shorter reaction times and lower reaction temperatures.

Methylation reactions via [<sup>11</sup>C]methyl iodide or [<sup>11</sup>C]methyl triflate are the most important routes for <sup>11</sup>C labelling reactions. There are two principal pathways available for the synthesis of [<sup>11</sup>C]methyl iodide, which is also the precursor for the synthesis of [<sup>11</sup>C]methyl triflate. The starting materials are either [<sup>11</sup>C]carbon dioxide generated in the target chamber using the <sup>14</sup>N(p,α)<sup>11</sup>C nuclear reaction on nitrogen in the presence of traces of oxygen [6.10], or via [<sup>11</sup>C]methane, which can be obtained either using the same nuclear reaction or nitrogen in the presence of hydrogen [6.11]. The ‘wet’ method of conversion of [<sup>11</sup>C]carbon dioxide usually involves reducing the CO<sub>2</sub> to methanol using lithium aluminium hydride (LiAlH<sub>4</sub>), and hydrolysis of the aluminium methoxate by phosphoric acid. The [<sup>11</sup>C]methanol can then be converted to [<sup>11</sup>C]methyl iodide using aqueous hydrogen iodide [6.12]. These procedures are known as ‘wet’ chemistry methods. In contrast to the wet method, the conversion of [<sup>11</sup>C]methane is performed via a gas phase reaction using elemental iodine as either a single or multipass method [6.12, 6.13]. The gas phase reaction is, in general, preferred over the wet method, since the SA is generally higher, without taking the extensive precautions required for the wet method.

## 6.7. PRECURSORS

In general, the synthesis of radiotracers begins with a small precursor molecule which is then incorporated into a larger molecule that is the radiotracer. Since these precursors must be made, for the most part, starting with carbon dioxide or methane, the number of possibilities is rather small. The reason for this is that the cyclotron gas target consists of a highly ionized gas where thermally and electronically excited atoms and molecules interact in an environment where there is plenty of energy available to overcome almost all chemical reaction activation barriers. As a result, the chemical form of the final product in the target will be determined by thermodynamics. For <sup>11</sup>C, the final product in an oxidizing environment is carbon dioxide (CO<sub>2</sub>) and in a reducing environment, the most stable is usually methane (CH<sub>4</sub>). These two chemical forms are then the building blocks of more complex molecules. For <sup>13</sup>N, the chemical form is determined

mainly by the phase in which the reaction is carried out. In the gas phase, nitrogen is the most stable molecular form and is, therefore, often the final product for the same reasons we examined in the carbon target. Since nitrogen gas is very unreactive, a gas target is rarely used for production of  $^{13}\text{N}$ . In an aqueous environment without added radical scavengers, the final product is usually  $[^{13}\text{N}]\text{NO}_3^-$ . In a gaseous target for the production of  $^{15}\text{O}$ , the usual form is  $^{15}\text{O}_2$  which can easily be converted into other chemical forms. In an aqueous environment, the  $^{15}\text{O}$  will rapidly exchange with the oxygen in water and that will become the final chemical form. For  $^{18}\text{F}$ , the usual product out of the target is usually either the fluoride ion ( $\text{F}^-$ ) or fluorine gas ( $\text{F}_2$ ), depending on the chemical environment in the target during irradiation. Each of these radionuclides has a variety of production pathways and nuclear reactions using protons, deuterons,  $^3\text{He}$  or alpha particles can be utilized. In most instances, however, a reaction involving protons is used. This is due in part to the fact that most PET cyclotrons have protons readily available.

### 6.7.1. $^{11}\text{C}$ labelled precursors

The most common method for the production of  $^{11}\text{C}$  is to use a nitrogen gas target and the  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$  nuclear reaction [6.10]. A trace of oxygen is required to ensure that the chemical form is  $\text{CO}_2$  and, therefore, a trace of oxygen is often added to the target before irradiation. Since  $\text{CO}_2$  is the most common precursor coming out of the target, many syntheses of  $^{11}\text{C}$  containing compounds use  $[^{11}\text{C}]\text{CO}_2$  as the first species. A number of other precursor molecules, some of which are shown in Fig. 6.2, are synthesized from labelled  $\text{CO}_2$ , after some synthetic manipulation once they are out of the cyclotron target.  $[^{11}\text{C}]\text{methane}$  is another precursor molecule that can be very useful in a variety of syntheses.  $[^{11}\text{C}]\text{methane}$  can be produced directly in the cyclotron target by adding hydrogen gas to the nitrogen target gas, or more commonly, is converted to methane from carbon dioxide by reduction. Another common precursor is  $[^{11}\text{C}]\text{cyanide}$ . Some of the earliest syntheses with  $^{11}\text{C}$  depended on  $[^{11}\text{C}]\text{CO}_2$  and  $[^{11}\text{C}]\text{cyanide}$  [6.14]. Today, however, the majority of  $[^{11}\text{C}]\text{radiotracer}$  syntheses rely on  $[^{11}\text{C}]\text{methyl iodide}$  as the means to introduce  $^{11}\text{C}$  into an organic molecule [6.12]. Reduction of carbon dioxide with either lithium aluminum hydride (which leads to methanol) or with hydrogen over a nickel catalyst (which leads to methane) is commonly used and is very reliable. There are commercial units specifically designed to carry out these reactions. Hydrogen iodide reacts with the  $[^{11}\text{C}]\text{methanol}$  to form  $[^{11}\text{C}]\text{methyl iodide}$ .  $[^{11}\text{C}]\text{Methane}$  gas can be passed through a heated tube containing gaseous iodine resulting in the formation of  $[^{11}\text{C}]\text{methyl iodide}$  which is extracted. The system can be a single pass or a recirculating system where the methyl iodide is removed after each pass through

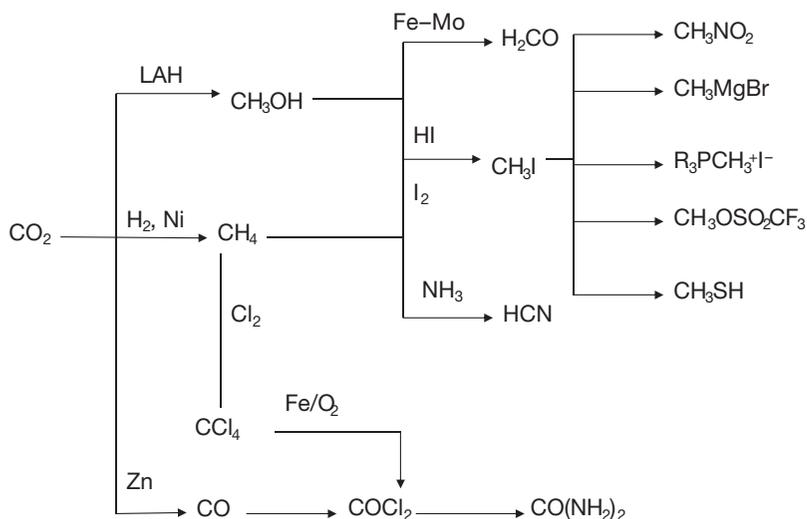


FIG. 6.2. Synthetic scheme for  $^{11}\text{C}$  precursors from gas targets.

the furnace. A complete listing of most PET labelled compounds as of 2004, classified according to compound type, with references and structures is available in Ref. [6.15].

SA is extremely important for a variety of radiotracers, especially those with specific targets which can be saturated with an excess of radiotracer mass. SA is defined as the fraction of radiolabelled molecules relative to the total number of molecules, and is usually expressed as a unit of radioactivity per mole of compound. According to the principles of tracers laid out by George Hevesy, it is important not to perturb the system you are trying to measure. When trying to probe the number of receptors or the concentration of an enzyme, these considerations become very important [6.16]. There is, of course, an ultimate limit to SA when there is nothing but the radioactive atoms or radiolabelled molecules. The characteristics of the four PET isotopes are shown in Table 6.2 [6.17]. In practice, however, these limits are rarely approached. As an example, the typical SAs for  $^{11}\text{C}$  labelled molecules are on the order of 1–100 Ci/ $\mu\text{mol}$  (37–3700 GBq/ $\mu\text{mol}$ ). Hence, it can be seen that at an SA of 370 GBq/ $\mu\text{mol}$ , only 1 in 1000 tracer molecules is actually labelled with  $^{11}\text{C}$ .

A promising new  $^{11}\text{C}$  reagent, [ $^{11}\text{C}$ ]methyl triflate, has recently been reported. This reagent has been prepared by the reaction of [ $^{11}\text{C}$ ]methyl iodide and silver triflate. It is more reactive than methyl iodide and can be used to label a variety of compounds.

TABLE 6.2. CHARACTERISTICS OF THE FOUR MAJOR PET RADIONUCLIDES

Isotope	Half-life (min)	$\beta^+$ endpoint energy MeV (% $\beta^+$ )	Theoretical specific activity (Ci/ $\mu$ mol)	Theoretical specific activity (TBq/ $\mu$ mol)
C-11	20.4	0.96 (100%)	9200	340
N-13	10	1.2 (100%)	18 800	696
F-18	110	0.6 (97%)	1700	63
O-15	2	1.73 (100%)	94 000	3478

### 6.7.2. $^{13}\text{N}$ labelled precursors

There are three nuclear reactions commonly used to produce  $^{13}\text{N}$ . These are the  $^{13}\text{C}(\text{p},\text{n})^{13}\text{N}$  reaction, using isotopically enriched carbon powder [6.18, 6.19], the  $^{12}\text{C}(\text{d},\text{n})^{13}\text{N}$  reaction, using natural carbon powder [6.20], and the  $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$  reaction, using natural water [6.21]. Most  $^{13}\text{N}$  containing compounds are synthesized using either nitrate ion from the water target or ammonia from the carbon powder targets. The ion  $[^{13}\text{N}]\text{NO}_3^-$  obtained from the water target can easily be converted into  $[^{13}\text{N}]$ ammonia using a reduction with DeVarda's alloy [6.22] or with titanium chloride [6.23].

### 6.7.3. $^{15}\text{O}$ labelled precursors

Oxygen-15 is commonly produced using the  $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$  reaction on enriched  $^{15}\text{N}$  or the  $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$  reaction on natural nitrogen gas. If SA is not a concern, the  $^{16}\text{O}(\text{p},\text{pn})^{15}\text{O}$  reaction can also be used. When nitrogen and oxygen are irradiated together, the oxides of nitrogen are produced directly [6.24]; a mixture of hydrogen and oxygen will produce labelled water under irradiation conditions [6.25]. These precursors can then be used to synthesize other  $^{15}\text{O}$  containing compounds.

### 6.7.4. $^{18}\text{F}$ labelled precursors

Two nuclear reactions are commonly used to produce  $^{18}\text{F}$  [6.26]. The first is the  $^{20}\text{Ne}(\text{d}, \alpha)^{18}\text{F}$  reaction carried out in a neon gas target. In order to keep the  $^{18}\text{F}$  from reacting completely with the walls of the target,  $\text{F}_2$  is added to keep the fluorine as molecular fluorine. The molecular fluorine ( $\text{F}_2$ ) can be used directly to synthesize  $[^{18}\text{F}]$ radiotracers [6.27]. The second reaction is the  $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$  nuclear

reaction on  $^{18}\text{O}$  enriched  $\text{O}_2$  (gas target) or on  $^{18}\text{O}$  enriched water (water target). In the case of the gas target, the  $^{18}\text{F}$  can be recovered either as a fluoride ion or as  $\text{F}_2$ . During irradiation, the  $^{18}\text{F}$  will be adsorbed on the walls of the target body since there is no  $\text{F}_2$  to keep it in the gas phase. If the intent is to recover  $^{18}\text{F}$  as  $\text{F}_2$ , after irradiation  $^{18}\text{O}$  enriched  $\text{O}_2$  is removed and the target filled with a mixture of a trace amount of  $\text{F}_2$  in an inert carrier gas such as argon [6.28]. The target is irradiated again for a short time during which the fluorine in the gas phase and the  $^{18}\text{F}$  on the walls of the target undergo isotopic exchange and the resulting mixture of  $^{18}\text{F}\text{F}_2$  in argon is removed and used for synthesis. For the water target, the activity is removed in the aqueous phase in the chemical form of a fluoride ion. One can use the  $^{18}\text{O}$  water containing  $^{18}\text{F}$  fluoride ion directly for synthesis and this method is used by those who have small volume water targets, and the cost of losing the  $^{18}\text{O}$  water is minor compared to the cost of the cyclotron run. Another method is to separate the  $^{18}\text{F}$  fluoride from the  $^{18}\text{O}$  water, either by distillation or by using a resin column [6.29–6.31]. When the resin is used, it also removes the metal ion impurities from the enriched fluoride solution which, in general, increases the reactivity of the fluoride. The fluoride can be made more reactive by combining it with a metal ion complexing agent, such as a crown ether or tetrabutylammonium salts [6.32].

## 6.8. MAINTENANCE

The maintenance schedule for gas targets is relatively simple. The front foil is the usual failure mode and this should be inspected often for signs of damage. If there are small bulges in the foil, it should be replaced. The two different kinds of foil commonly used on gas targets are aluminium and Havar, and they have very different characteristics. Aluminium foils often deteriorate slowly, with a small leak developing first, and then the leak becoming larger until the foil fails. Havar foils, on the other hand, often fail with no warning. To minimize radiation dose, the best time for inspection is after an extended period of no beam on the target when the foil has had a chance to decay. In those facilities that operate 5 days a week, this would be after the weekend, on the first work day of the week (Table 6.3).

Occasionally, it may be necessary to clean the interior of the gas target. There are several procedures, used by different centres, to clean the  $^{11}\text{C}$  gas targets. A survey of these procedures on polished aluminium targets, and the results, are shown below:

- Cleaning using isopropyl alcohol, rinsed repeatedly with deionized water and bake out. This procedure is done every 1–2 years.

TABLE 6.3. SUGGESTED MAINTENANCE SCHEDULE FOR GAS TARGETS

Frequency	Procedure
Weekly	Visually check for damaged tubing or fittings Leak check the system Check front foil for signs of damage
Monthly	Test plastics for radiation damage Track target yields to establish trends

- Window and O-ring change when there is a leak. Maintenance is done as infrequently as possible, since the yield drops every time the target is exposed to the atmosphere.
- No regular maintenance. In the case of target failure, surface cleaning and isolation checking are carried out.
- The target requires no maintenance except foil changes and occasionally, at that time, a manual dry scrubbing of a bit of white buildup inside.
- Maintenance is performed every 3 months or when the integrated current >2000  $\mu\text{A}/\text{h}$ . At that time, the window and O-rings are changed, and the target is cleaned inside with water and ethyl alcohol and dried.
- Once per year, the target foils and O-rings are replaced. No attempt is made to clean the inside surfaces

As can be seen from these responses, the basic attitude is to leave the target working unless it fails. Routine changing of the foils is an option, although people who use thicker aluminium foils and metal O-rings often go for several years without any maintenance at all.

#### REFERENCES TO SECTION 6

- [6.1] EHRIN, L., GAWELL, T., HOGBERG, T., DE PAULIS, P., STROM, J., Synthesis of [methoxy- $^3\text{H}$ ] and [methoxy- $^{11}\text{C}$ ] labelled raclopride: Specific D2 receptor ligand, *J. Labelled Compd. Rad.* **24** (1987) 931
- [6.2] HELIN, S., ARPONEN, E., RAJANDER, J., AROMAA, J., SOLIN, O., “Target performance – [ $^{11}\text{C}$ ]CO<sub>2</sub> and [ $^{11}\text{C}$ ]CH<sub>4</sub> production”, *Proc. 13th Workshop on Targetry and Target Chemistry (WTTC)*, Copenhagen (2010).
- [6.3] NICKLES, R.J., DAUBE, M.E., RUTH, T.J., An  $^{18}\text{O}_2$  target for the production of  $^{18}\text{F}_2$ , *Appl. Radiat. Isotopes* **35** (1984) 117–122.
- [6.4] HUGHES, C., et al., A simple and highly sensitive spectrophotometric method for the determination of cyanide in equine blood, *Toxicol. Mech. Method.* **13** (2003) 129–138.

- [6.5] CHRISTISON, T.T., ROHRER, J.S., Direct determination of free cyanide in drinking water by ion chromatography with pulsed amperometric detection, *J. Chromatogr. A* **1155** (2007) 31–39.
- [6.6] LAMBERT, J.L., RAMASAMY, J., PAUKSTELLS, J., Stable reagents for colorimetric determination of cyanide by modified Konig reactions, *Anal. Chem.* **47** (1975) 916–918.
- [6.7] O'DELL, J.W. (Ed.), Method 353.2: Determination of Nitrate-Nitrite Nitrogen by Automated Colorimetry, U.S. Environmental Protection Agency, Cincinnati, Ohio (1993), <http://www.dec.state.ak.us/eh/docs/lab/dw/Chem/inorganics/353.2.pdf>
- [6.8] LANDAIS, P., FINN, R., On-line preparation of [<sup>11</sup>C]carbon dioxide from [<sup>11</sup>C]methane, *Appl. Radiat. Isotopes* **40** (1989) 265–266.
- [6.9] SMITH, R.D., et al., Optimization of [<sup>11</sup>C]CO<sub>2</sub> trapping efficiencies from nitrogen gas streams, *Appl. Radiat. Isotopes* **43** (1992) 466–468.
- [6.10] CHRISTMAN, D.R., FINN, R.D., KARLSTROM, K.I., WOLF, A.P., The production of ultra high activity <sup>11</sup>C-labelled hydrogen cyanide, carbon dioxide, carbon monoxide, and methane via the <sup>14</sup>N(p, α)<sup>11</sup>C reaction, *Appl. Radiat. Isotopes* **26** (1975) 435–442.
- [6.11] HELUS, F., HANISCH, M., LAYER, K., MAIER-BORST, W., Yield ratio of <sup>11</sup>C-CO<sub>2</sub>, <sup>11</sup>C-CO, and <sup>11</sup>C-CH<sub>4</sub> from the irradiation of N<sub>2</sub>H<sub>2</sub> mixtures in the gas target, *J. Labelled Compd. Rad.* **23** (1986) 1202–1205.
- [6.12] LANGSTROM, B., LUNDQVIST, H., The preparation of [<sup>11</sup>C]methyl iodide and its use in the synthesis of [<sup>11</sup>C]methyl-L-methionine, *Appl. Radiat. Isotopes* **27** (1976) 357–363.
- [6.13] LINK, J.M., KROHN, K.A., CLARK, J.C., Production of [C-11]CH<sub>3</sub>I by single pass reaction of [C-11]CH<sub>4</sub> with I<sub>2</sub>, *Nucl. Med. Biol.* **24** (1997) 93–97.
- [6.14] FINN, R.D., CHRISTMAN, D.R., ACHE, H.J., WOLF, A.P., The preparation of cyanide-<sup>11</sup>C for use in the synthesis of organic radiopharmaceuticals II, *Appl. Radiat. Isotopes* **22** (1971) 735–744.
- [6.15] IWATA, R., Reference Book for PET Radiopharmaceuticals, Cyclotron and Radioisotope Center, Tohoku University, Japan (2004).
- [6.16] DANNALS, R., RAVERT, H.T., WILSON, A.A., WAGNER, H.N., “Special problems associated with the synthesis of high specific activity carbon-11 labelled radiotracers”, *New Trends in Radiopharmaceutical Synthesis, Quality Assurance and Regulatory Control* (EMRAN, A.M., Ed.), Plenum Press, New York (1991) 21–30.
- [6.17] FOWLER, J.S., WOLF, A.P., Working against time: rapid radiotracer synthesis and imaging the human brain, *Accts. Chem. Res.* **30** (1997) 181–188.
- [6.18] FERRIERI, R.A., SCHLYER, D.J., WIELAND, B.W., WOLF, A.P., On-line production of <sup>13</sup>N-nitrogen gas from a solid enriched <sup>13</sup>C-target and its application to <sup>13</sup>N-ammonia synthesis using microwave radiation, *Appl. Radiat. Isotopes* **34** (1983) 897–900.
- [6.19] BIDA, G., et al., An economical target for <sup>13</sup>N production by proton bombardment of a slurry of <sup>13</sup>C powder on <sup>16</sup>O water, *J. Labelled Compd. Rad.* **23** (1986) 1217–1218.
- [6.20] DENCE, C.S., WELCH, M.J., HUGHEY, B.J., SHEFER, R.E., KLINKOWSTEIN, R.E., Production of [<sup>13</sup>N] ammonia applicable to low energy accelerators, *Nucl. Med. Biol.* **21** (1994) 987–996.
- [6.21] PARKS, N.J., KROHN, K.A., The synthesis of <sup>13</sup>N labelled ammonia, dinitrogen, nitrite, nitrate using a single cyclotron target system, *Appl. Radiat. Isotopes* **29** (1978) 754–757.

- [6.22] VAALBURG, W., KAMPHUIS, J.A., BEERLING-VAN DER MOLEN, H.D., RIJSKAMP, A., WOLDRING, M.G., An improved method for the cyclotron production of  $^{13}\text{N}$ -labelled ammonia, *Appl. Radiat. Isotopes* **26** (1975) 316–318.
- [6.23] IDO, T., IWATA, R., Fully automated synthesis of  $^{13}\text{NH}_3$ , *J. Labelled Compd. Rad.* **18** (1981) 244–246.
- [6.24] CLARK, J.C., BUCKINGHAM, P.D., *Short-lived Radioactive Gases for Clinical Use*, Butterworths, London (1975).
- [6.25] VERA-RUIZ, H., WOLF, A.P., Direct synthesis of oxygen-15 labelled water of high specific activity, *J. Labelled Compd. Rad.* **15** (1978) 186–189.
- [6.26] HELUS, F., MAIER-BORST, W., SAHM, U., WIEBE, L.I., F-18 cyclotron production methods, *Radiochem. Radioa. Let.* **38** (1979) 395–410.
- [6.27] LAMBRECHT, R.M., NEIRINCKX, R., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals XXIII: novel anhydrous  $^{18}\text{F}$ -fluorinating intermediates, *Appl. Radiat. Isotopes* **29** (1978) 175–183.
- [6.28] NICKLES, R.J., HICHTWA, R.D., DAUBE, M.E., HUTCHINS, G.D., CONGDON, D.D., An  $^{18}\text{O}$ -target for the high yield production of  $^{18}\text{F}$ -fluoride, *Appl. Radiat. Isotopes* **34** (1983) 625–629.
- [6.29] SCHLYER, D.J., BASTOS, M.A., ALEXOFF, D., WOLF, A.P., Separation of [ $^{18}\text{F}$ ]fluoride from [ $^{18}\text{O}$ ]water using anion exchange resin, *Appl. Radiat. Isotopes* **41** (1990) 531–533.
- [6.30] MOCK, B.H., VAVREK, M.T., MULHOLLAND, G.K., Back-to-back “one-pot” [ $^{18}\text{F}$ ]FDG syntheses in a single Siemens-CTI chemistry process control unit, *Nucl. Med. Biol.* **23** (1996) 497–501.
- [6.31] PASCALI, C., et al., A convenient semi-automated system for optimizing the recovery of aqueous [ $^{18}\text{F}$ ]fluoride from target, *Proc. 7th Int. Workshop on Targetry and Target Chemistry (WTTC)*, Heidelberg (1997).
- [6.32] HAMACHER, K., COENEN, H.H., STOCKLIN, G., Efficient stereospecific synthesis of no-carrier-added 2- [ $^{18}\text{F}$ ]fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution, *J. Nucl. Med.* **27** (1986) 235–238.

## 7. CONCLUSIONS

During the past 30 years, since the time of the first delivery of FDG to a PET camera, there have been very dramatic changes in the production of radionuclides. The number of cyclotrons in the world has blossomed, so that at the time of writing there are more than 750 cyclotrons devoted to the production of radionuclides for PET and SPECT nuclear medicine studies. During this time, the study of cyclotron targetry has gone through several stages of development. The fluorine gas target has gone from a simple nickel pipe used in 1975 to make the first  $F_2$  for FDG from the  $^{20}\text{Ne}(p,\alpha)^{18}\text{F}$  nuclear reaction on neon gas with added  $F_2$ , to very sophisticated shapes that take into account the multiple scattering in the front foil and the thermal gradient set up along the beam path and using the  $^{18}\text{O}(p,n)^{18}\text{F}$  reaction on  $^{18}\text{O}$  enriched oxygen gas in the two shoot method.

During that same time, the water target has gone from making  $[^{13}\text{N}]$  ammonia to a  $^{18}\text{O}$  enriched water target for making  $[^{18}\text{F}]$  fluoride ion. The development of the chemistry to make FDG from fluoride was a turning point in the use of FDG, as it made it possible to make substantial amounts for the first time.

The following questions that led to the production of this book have been addressed herein but others require some additional research.

### **Which targets are currently important to the user community and are likely to be important in the near future?**

It is clear that the main targets for now and in the near future are the targets for  $^{18}\text{F}$ ,  $^{11}\text{C}$  and  $^{13}\text{N}$ . Oxygen-15 has fallen out of favour in most centres, due to the availability of blood oxygen level dependent studies carried out with magnetic resonance imaging. Although not identical, the magnetic resonance imaging studies give similar information and are somewhat easier to accomplish.

### **Which targets are currently underdeveloped and need further research to achieve their potential? How can new targets be developed to withstand higher beam current and, therefore, utilize the full capabilities of modern cyclotrons?**

The water target is by far the most widely used target, and an area of avid interest is trying to build water targets that will withstand beam currents of more than  $100\ \mu\text{A}$  for long periods of time, allowing the commercial producers to increase their output. There are several approaches to this goal, most of which

allow very rapid boiling of the water in the target or rapid recirculation of the water. As the price of highly enriched water increases, the former approach becomes more attractive, since it uses significantly less water than even the most efficient recirculating water targets.

### **What research can be done to improve performance in targets?**

The primary goal in high power water targets and gas targets is the removal of heat. Novel engineering methods to increase the heat removal characteristics need to be an active area of research. New materials or new mechanical designs utilizing the geometry of the beam on the target offer some potential solutions.

### **How can novel methods of producing the product or precursor ‘on-line’ such as the use of ‘in-target’ chemistry be improved to produce the desired product?**

Significant research has been carried out on the production of  $[^{11}\text{C}]\text{CH}_4$  directly in the target. This method of production can, in principle, increase the SA of the final product. Different target materials and irradiation parameters have been examined. Other precursors that might be produced in-target include CO and HCN.

### **How can the recovery/recycle chemistries of enriched target materials be refined?**

This is an area of ongoing research, with new methods for separation of the enriched target material from the product radionuclide. Methods include column extraction and electrochemistry. As these methods improve, they should provide higher recoveries of the expensive enriched isotopes required for the production of some radionuclides.

### **How can it be ensured that recycled materials will meet production standards?**

Careful quality control testing of recycled material is required. As an example, the  $^{18}\text{O}$  enriched water used for the production of  $^{18}\text{F}$  may be recycled, but care must be taken to ensure that all organic, inorganic and radionuclidic impurities are removed before the water is used again for production. There are significant GMP compliance issues associated with the recycling if the  $^{18}\text{F}$  produced is being used for the synthesis of radiopharmaceuticals for human use.

As the price of  $^{18}\text{O}$  enriched water increases, the option of using recycled water becomes more attractive.

### **How can methods be developed for quality control of the pre-irradiation target?**

For solid targets, there are already some tests that can be carried out. However, for gas and liquid targets, the situation is more difficult. In some centres, short irradiations are carried out on the targets before the production beam, to ensure that everything is operating as expected. The gases or liquids being used may have to meet certain specifications if the final product has to meet GMP requirements.

### **How can target diagnostics be used during irradiation?**

Instrumentation needs to be developed that can monitor such factors as power dissipation, temperature, pressure, radionuclide production rate, beam position, etc. Some development has taken place, but there is still a significant need for simple in-beam diagnostic devices that can give warning if there is a problem with the beam position or intensity distribution.

### **How can beam entry windows for gas targets be improved? What material properties are most important?**

The expected demands of the new high current targets will demand exploration of new materials and techniques. The engineering aspects of target development are becoming more important as the power levels required increase. As we go above  $100\ \mu\text{A}$ , the power can reach almost 2 kW. This level of power dissipation is a challenge for the new generation of target designers. The materials and guidance in this publication should help designers optimize their target designs.

### **How can current research be extended to make it most useful to the radionuclide production community?**

There is a clear need for training at all levels of experience and expertise in this field. Training visits to operating facilities are a valuable option. The opportunities for long distance learning are also increasing. Contributions to this area should be open to all centres.



## BIBLIOGRAPHY

### Radionuclides

HELUS, F., et al., Contribution to the cyclotron targetry, *J. Radioan. Nucl. Ch.* **198** (1995) 247–252.

KOVÁCS, Z., et al., Excitation functions for the formation of some radioisotopes of rubidium in proton induced nuclear reactions on  $^{nat}\text{Kr}$ ,  $^{82}\text{Kr}$  and  $^{83}\text{Kr}$  with special reference to the production of  $^{81}\text{Rb}$ ( $^{81m}\text{Kr}$ ) generator radionuclide, *Appl. Radiat. Isotopes* **42** (1991) 329–335.

LAMBRECHT, R.M., NEIRINCKX, R., WOLF A.P., Cyclotron isotopes and radiopharmaceuticals — XXIII: Novel anhydrous  $^{18}\text{F}$ -fluorinating intermediates, *Appl. Radiat. Isotopes* **29** (1978) 175–183.

LLOP, J., et al., Synthesis of S- $^{13}\text{N}$ ]nitrosogluthione ( $^{13}\text{N}$ -GSNO) as a new potential PET imaging agent, *Appl. Radiat. Isotopes* **67** (2009) 95–99.

NICKLES, R.J., A shotgun approach to the chart of the nuclides: radiotracer production with an 11 MeV proton cyclotron, *Acta Radiol. Suppl.* **376** (1991) 69–71.

POLICRONIADES, R., et al., F-18 production by means of  $^{20}\text{Ne}(d,^4\text{He})$  reaction at ININ, *Rev. Mex. Fis.* **54** Suppl. 1 (2008) 46–49.

SAJJAD, M., LAMBRECHT, R.M., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals XXXIV: Excitation function for the  $^{15}\text{N}(p,n)^{15}\text{O}$  reaction, *Radiochim. Acta* **36** (1984) 159.

SAJJAD, M., LAMBRECHT, R.M., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals XXXVI: Investigation of some excitation functions for the preparation of  $^{15}\text{O}$ ,  $^{13}\text{N}$  and  $^{11}\text{C}$ , *Radiochim. Acta* **38** (1985) 57–63.

SUMIYA, C.A., SCIANI, V., Evaluation of irradiation parameters of enriched  $^{124}\text{Xe}$  target for  $^{123}\text{I}$  production in cyclotrons, *Appl. Radiat. Isotopes* **66** (2008) 1337–1340.

TAKÁCS, S., TÁRKÁNYI, F., HERMANNE, A., PAVIOTTI DE CORCUERA, R., Validation and upgrading of the recommended cross section data of charged particle reactions used for production of PET radioisotopes, *Nucl. Instrum. Meth. B* **211** 2 (2003) 169–189.

TÁRKÁNYI F., et al., Excitation functions of (p,2n) and (p,pn) reactions and differential and integral yields of  $^{123}\text{I}$  in proton induced nuclear reactions on highly enriched  $^{124}\text{Xe}$ , *Appl. Radiat. Isotopes* **42** (1991) 221–228.

## **[<sup>18</sup>O]water — <sup>18</sup>F**

ALVORD, C.W., WILLIAMSON, A.C., GRAVES, T.L., ZIGLER, S.S., Design, test and widespread implementation of a compact kilo-watt fluoride ion target, *Nucl. Instrum. Meth. B* **241** (2005) 708–712.

EHRENKAUFER, R.E., et al., Production of H<sup>18</sup>F by deuteron irradiation of a neon-hydrogen gas target, *Radiochim. Acta* **33** (1983) 49–56.

HONG, B.H., et al., Pleated double-foil O-18 water target, *Nucl. Instrum. Meth. B* **261** (2007) 813–815.

HUR, M.G., The study of proton beam irradiated H<sub>2</sub><sup>18</sup>O water target, *Nucl. Instrum. Meth. B* **241** (2005) 735–737.

IWATA, R., IDO, T., BRADY, F., TAKAHASHI, T., UJIIE, A., [<sup>18</sup>F]fluoride production with a circulating [<sup>18</sup>O]water target, *Appl. Radiat. Isotopes* **38** (1987) 979–984.

KEINONEN, J., FONTELL, A., KAIRENTO, A.L., Effective small-volume [<sup>18</sup>O] water target for the production of [<sup>18</sup>F]fluoride, *Appl. Radiat. Isotopes* **37** (1986) 631–632.

KILBOURN, M.R., HOOD, J.T., WELCH, M.J., A simple <sup>18</sup>O water target for <sup>18</sup>F production, *Appl. Radiat. Isotopes* **35** (1984) 599.

KILBOURN, M.R., JERABEK, P.A., WELCH, M.J., An improved [<sup>18</sup>O]water target for [<sup>18</sup>F]fluoride production, *Appl. Radiat. Isotopes* **36** (1985) 327–328.

KNUST, E.J., MACHULLA, H.J., High yield production of <sup>18</sup>F in a water target via the <sup>16</sup>O(<sup>3</sup>He,p)<sup>18</sup>F reaction, *Appl. Radiat. Isotopes* **34** (1983) 1627–1628.

MIRZAI, M., AFARIDEH, H., HADJI-SAEID, S.M., ASLANI, G.R., ENSAF, M.R., Production of [<sup>18</sup>F] fluoride with a high-current two layer spherical gold target, *Nukleonika* **49** (2004) 23–27.

RUTH, T.J., WOLF, A.P., Absolute cross section for the production of F-18 via the <sup>18</sup>O(p,n)<sup>18</sup>F reaction, *Radiochim. Acta* **26** (1979) 21–24.

RUTH, T.J., et al., A proof of principle for the targetry to produce ultra-high quantities of <sup>18</sup>F-fluoride, *Appl. Rad. Isotopes* **55** (2001) 457–461.

SATYAMURTHY, N., AMARASEKERA, B., ALVORD, C.W., BARRIO, J.R., PHELPS, M.E., Tantalum [<sup>18</sup>O]water target for the production of [<sup>18</sup>F]fluoride with high reactivity for the preparation of 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose, *Mol. Imaging Biol.* **4** (2002) 65–70.

SCHLYER, D.J., BASTOS, M.A., ALEXOFF, D., WOLF, A.P., Separation of [<sup>18</sup>F]fluoride from [<sup>18</sup>O]water using anion exchange resin, *Int. J. Rad. Appl. Instrum. A* **41** (1990) 531–533.

STEINBACH, J., et al., Temperature course in small volume [ $^{18}\text{O}$ ]water targets for [ $^{18}\text{F}$ ]F-production, *Int. J. Rad. Appl. Instrum. A* **41**(1990) 753–756.

TEWSON, T.J., BERRIDGE, M.S., BOLOMEY, L., GOULD, K.L., Routine production of reactive fluorine-18 salts from an oxygen-18 water target, *Nucl. Med. Biol.* **15** (1988) 499–504.

VOGT, M., HUSAR, I., OEHNINGER, H., WEINREICH, R., Improved production of [ $^{18}\text{F}$ ]fluoride via the [ $^{18}\text{O}$ ]H $_2$ O(p,n) $^{18}\text{F}$  reaction for no-carrier added nucleophilic syntheses, *Appl. Radiat. Isotopes* **37** (1986) 448–449.

ZEISLER, S.K., BECKER, D.W., PAVAN, R.A., MOSCHEL, R., RÜHLE, H., A water-cooled spherical niobium target for the production of [ $^{18}\text{F}$ ]fluoride, *Appl. Radiat. Isotopes* **53** (2000) 449–453.

### $^{20}\text{Ne}$ gas $^{18}\text{F}_2$

BIDA, G.T., et al., The effect of target gas purity on the chemical form of  $^{18}\text{F}$  during  $^{18}\text{F}\text{-F}_2$  production using the neon/fluorine (Ne/ $\text{F}_2$ ) target, *J. Nucl. Med.* **21** (1980) 758–762.

BLESSING, G., COENEN, H.H., FRANKEN, K., QAIM, S.M., Production of [ $^{18}\text{F}$ ]F $_2$ , H $^{18}\text{F}$  and  $^{18}\text{F}\text{-}_{\text{aq}}^-$  using the  $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$  process, *Appl. Radiat. Isotopes* **37** (1986) 1135–1139.

CASELLA, V., et al., Anhydrous F-18 labelled elemental fluorine for radiopharmaceutical preparation, *J. Nucl. Med.* **21** (1980) 750–757.

CROUZEL, C., COMAR, D., Production of carrier-free  $^{18}\text{F}$ -hydrofluoric acid, *Int. J. Appl. Radiat. Is.* **29** (1978) 407–408.

EHRENKAUFER, R.E., MACGREGOR, R.R., WOLF, A.P., RUTH, T.J., Production of H $^{18}\text{F}$  by deuteron irradiation of a neon-hydrogen gas target, *Radiochim. Acta* **33** (1983) 49–56.

HELUS, F., UHLIR, V., GASPER, H., Contribution to cyclotron targetry. 3. Behavior of radionuclides produced and co-produced via Ne-20(d, $\alpha$ )F-18 in the target chamber and in an electrical-field, *J. Radioanal. Nucl. Ch.* **196** (1995) 107–111.

HELUS, F., UHLIR, V., GASPER, H., WOLBER, G., MAIER-BORST, W., Contribution to the cyclotron targetry. 4. Measurement of F-18, Na-21, and Ne-23 production yields in deuteron induced reaction on neon gas, *J. Radioanal. Nucl. Ch.* **198** (1995) 247–252.

HELUS, F., UHLIR, V., WOLBER, G., GASPER, H., MAIER-BORST, W., Contribution to cyclotron targetry. 1. Distribution and quantification of F-18 activity produced via Ne-20(d, $\alpha$ )F-18 reaction in a gas-target, *J. Radioanal. Nucl. Ch.* **182** (1994) 237–245.

NOZAKI, T., IWAMOTO, M., IDO, T., Yield of  $^{18}\text{F}$  for various reactions from oxygen and neon, *Appl. Radiat. Isotopes* **25** (1974) 393–399.

WIELAND, B.W., SCHLYER, D.J., RUTH, T.J., WOLF, A.P., Deuteron beam penetration in a neon gas-target for producing F-18, *J. Labelled Compd. Rad.* **18** (1981) 27–29.

### **<sup>18</sup>O gas <sup>18</sup>F<sub>2</sub>**

BERGMAN, J., SOLIN, O., F-18 labelled fluorine gas for synthesis of tracer molecules, *Nucl. Med. Biol.* **24** (1997) 677–683.

BISHOP, A., et al., Proton irradiation of [<sup>18</sup>O]O<sub>2</sub>: production of [<sup>18</sup>F]F<sub>2</sub> and [<sup>18</sup>F]F<sub>2</sub> + [<sup>18</sup>F]OF<sub>2</sub>, *Nucl. Med. Biol.* **23** (1996) 189–199.

BISHOP, A., SATYAMURTHY, N., BIDA, G., Identification and quantitation of gaseous compounds of fluorine generated in [F-18]F-2 target systems, *Nucl. Med. Biol.* **23** (1996) 391–405.

BISHOP, A., SATYAMURTHY, N., BIDA, G., PHELPS, M., BARRIO, J.R., Metals suitable for fluorine gas target bodies: First use of aluminium for the production of [F-18]F-2, *Nucl. Med. Biol.* **23** (1996) 181–188.

DAUBE, M.E., NICKLES, R.J., RUTH, T.J., An <sup>18</sup>O<sub>2</sub> target for the production of [<sup>18</sup>F]F<sub>2</sub>, *Appl. Radiat. Isotopes* **35** (1984) 117–122.

REEDY, G.N., BEER, H.F., SCHUBIGER, P.A., “Determination of excitation functions for <sup>20</sup>Ne(p,2pn)<sup>18</sup>Ne→<sup>18</sup>F and <sup>20</sup>Ne(p,2pn)<sup>18</sup>F and a reexamination of production of [<sup>18</sup>F]F<sub>2</sub> with protons on neon”, *Proc. 5th Int. Workshop on Targetry and Target Chemistry (WTTC)*, New York (1993).

ROBERTS, A.D., OAKES, T.R., NICKLES, R.J., Development of an improved target for [<sup>18</sup>F]F<sub>2</sub> production, *Appl. Radiat. Isotopes* **46** (1995) 87.

RUTH, T.J., The production of <sup>18</sup>F-F<sub>2</sub> and <sup>15</sup>O-O<sub>2</sub> sequentially from the same target chamber, *Appl. Radiat. Isotopes* **36** (1985) 107–110.

RUTH, T.J., WOLF, A.P., Absolute cross section for the production of F-18 via the <sup>18</sup>O(p,n)<sup>18</sup>F reaction, *Radiochim. Acta* **26** (1979) 21–24.

### **<sup>14</sup>N gas <sup>11</sup>C**

BUCKLEY, K.R., HUSER, J., JIVAN, S., CHUN, K.S., RUTH, T.J., <sup>11</sup>C-methane production in small volume, high pressure gas targets, *Radiochim. Acta* **88** (2000) 201–205.

BUCKLEY, K.R., JIVAN, S., RUTH, T.J., Improved yields for the in situ production of [<sup>11</sup>C]CH<sub>4</sub> using a niobium target chamber, *Nucl. Med. Biol.* **31** (2004) 825.

CHRISTMAN, D.R., FINN, R.D., KARLSTROM, K.I., WOLF, A.P., The production of ultra high activity  $^{11}\text{C}$ -labeled hydrogen cyanide, carbon dioxide, carbon monoxide and methane via the  $^{14}\text{N}(p,\alpha)^{11}\text{C}$  reaction (XV), *Appl. Radiat. Isotopes* **26** (1975) 435–442.

FERRIERI, R.A., WOLF, A.P., The chemistry of positron emitting nucleogenic (hot) atoms with regard to preparation of labelled compounds of practical utility, *Radiochim. Acta* **34** (1983) 69.

HELUS, F., HANISCH, M., LAYER, K., MAIER-BORST, W., Yield ratio of  $^{11}\text{C}$ - $\text{CO}_2$ ,  $^{11}\text{C}$ - $\text{CO}$ , and  $^{11}\text{C}$ - $\text{CH}_4$  from the irradiation of  $\text{N}_2\text{H}_2$  mixtures in the gas target, *J. Labelled Compd. Rad.* **23** (1986) 1202–1205.

SUZUKI, K., YAMAZAKI, I., SASAKI, M., KUBODERA, A., Specific activity of  $^{11}\text{C}$ ] $\text{CO}_2$  generated in a  $\text{N}_2$  gas target: effect of irradiation dose, irradiation history, oxygen content and beam energy, *Radiochim. Acta* **88** (2000) 211.

VANDEWALLE, T., VANDECASTEELE, C., Optimisation of the production of  $^{11}\text{C}$ ] $\text{CO}_2$  by proton irradiation of nitrogen gas, *Appl. Radiat. Isotopes* **34** (1983) 1459–1464.

ZHANG, M.R., SUZUKI, K., Sources of carbon which decrease the specific activity of  $^{11}\text{C}$ ] $\text{CH}_3\text{I}$  synthesized by the single pass  $\text{I}_2$  method, *Appl. Radiat. Isotopes* **62** (2005) 447–450.

## **$^{16}\text{O}$ liquid $^{13}\text{N}$**

AUSTIN, S.M., GALONSKY, A., BORTINS, J., WOLK, C.P., A batch process for the production of  $^{13}\text{N}$ -labelled nitrogen gas, *Nucl. Instrum. Meth.* **126** (1975) 373–379.

BERRIDGE, M.S., LANDMEIER, B.J., In-target production of  $^{13}\text{N}$ ] ammonia: target design, products and operating parameters, *Appl. Radiat. Isotopes* **44** (1993) 1433–1441.

BIDA, G., SATYAMURTHY, N., “[ $^{13}\text{N}$ ]Ammonia production via proton irradiation of  $\text{CO}_2/\text{H}_2\text{O}$ : a work in progress”, *Proc. 6th Int. Workshop on Targetry and Target Chemistry (WTTC)*, Vancouver (1995) 189–191.

DENCE, C.S., WELCH, M.J., HUGHEY, B.J., SHEFER, R.E., KLINKOWSTEIN, R.E. Production of  $^{13}\text{N}$ ] ammonia applicable to low energy accelerators, *Nucl. Med. Biol.* **21** (1994) 987–996.

FIROUZBAKHT, M.L., SCHLYER, D.J., FERRIERI, R.A., WOLF, A.P., FOWLER, J.S., Mechanisms involved in the production of nitrogen-13-labeled ammonia in a cryogenic water target, *Nucl. Med. Biol.* **26** (1999) 437–441.

HELMEKE, H.J., HARMS, T., KNAPP, W.H., “Home-made routinely used targets for the production of PET radionuclides”, *Proc. 7th Int. Workshop on Targetry and Target Chemistry (WTTC)*, Heidelberg (1997) 241.

KORSAKOV, M.V., KRASIKOVA, R.N., FEDOROVA, O.S., Production of high yield [ $^{13}\text{N}$ ]ammonia by proton irradiation from pressurized aqueous solutions, *J. Radioan. Nucl. Ch.* **204** (1996) 231–239.

MCCARTHY, T.J., GAEHLE, G.G., MARGENAU, W.H., GURLEYIK, K., “Evaluation of a commercially available heater for the rapid combustion of graphite disks used in the production of [ $^{13}\text{N}$ ]NO and [ $^{13}\text{N}$ ]NO $_2$ ”, *Proc. 7th Int. Workshop on Targetry and Target Chemistry (WTTC), Heidelberg* (1997) 205.

MEDEMA, J., ELSINGA, P.H., KEIZER, H., FRANSSSEN, E.J.F., VAALBURG, W., “Remote controlled in-target production of [ $^{13}\text{N}$ ]ammonia using a circulating target”, *Proc. 7th Int. Workshop on Targetry and Target Chemistry (WTTC), Heidelberg* (1997) 80.

MIKECZ, P., DOOD, M.G., CHALONER, F., SHARP, P.F., “Glass target for production of [ $^{13}\text{N}$ ]NH $_3$  from methane, revival of an old method”, *Proc. 7th Int. Workshop on Targetry and Target Chemistry (WTTC), Heidelberg* (1997) 163.

MULHOLLAND, G.K., KILBOURN, M.R., MOSKWA, J.J., Direct simultaneous production of [ $^{15}\text{O}$ ]water and [ $^{13}\text{N}$ ]ammonia or [ $^{18}\text{F}$ ]fluoride ion by 26 MeV proton irradiation of a double chamber water target, *Appl. Radiat. Isotopes* **41** (1990) 1193–1199.

PARKS, N.J., KROHN, K.A., The synthesis of  $^{13}\text{N}$  labelled ammonia, dinitrogen, nitrite, nitrate using a single cyclotron target system, *Appl. Radiat. Isotopes* **29** (1978) 754–757.

PATT, J.T., NEBLING, B., STOCKLIN, G., Water target chemistry of nitrogen-13 recoils revisited, *J. Labelled Compd. Rad.* **30** (1991) 122–123.

SAJJAD, M., LAMBRECHT, R.M., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals XXXVII: excitation functions for the  $^{16}\text{O}(p,\alpha)^{13}\text{N}$  and  $^{14}\text{N}(p,pn)^{13}\text{N}$  reactions, *Radiochim. Acta* **39** (1986) 165–168.

SASAKI, M., HARADAHIRA, T., SUZUKI, K., Effect of dissolved gas on the specific activity of N-13 labelled ions generated in water by the  $^{16}\text{O}(p,\alpha)^{13}\text{N}$  reaction, *Radiochim. Acta* **88** (2000) 217–220.

STRAATMANN, M.G., A look at  $^{13}\text{N}$  and  $^{15}\text{O}$  in radiopharmaceuticals, *Appl. Radiat. Isotopes* **28** (1977) 13–20.

STRAATMANN, M.G., WELCH, M.J., Enzymatic synthesis of nitrogen-13 labelled amino acids, *Radiat. Res.* **56** (1973) 48–56.

TILBURY, R.S., DAHL, J.R.,  $^{13}\text{N}$  Species formed by the proton irradiation of water, *Radiat. Res.* **79** (1979) 22–33.

TILBURY, R.S., DAHL, J.R., MARANO, S.J., N-13 species formed by proton irradiation of water, *J. Labelled Compd. Rad.* **13** (1977) 208.

TILBURY, R.S., EMRAN, A.M., “[<sup>13</sup>N] Labeled tracers, synthesis and applications”, *New Trends in Radiopharmaceutical Synthesis, Quality Assurance, and Regulatory Control* (EMRAN E., Ed.), Plenum Press, New York (1991) 39–51.

VAALBURG, W., et al., Production of <sup>13</sup>N-labelled molecular nitrogen for pulmonary function studies, *J. Labelled Compd. Rad.* **18** (1981) 303–308.

WELCH, M.J., Production of active molecular nitrogen by the reaction of recoil nitrogen-13, *Chem. Commun.* (1968) 1354–1355.

WIELAND, B.W., et al., In-target production of [<sup>13</sup>N] ammonia via proton irradiation of dilute aqueous ethanol and acetic acid mixtures, *Appl. Radiat. Isotopes* **42** (1991) 1095–1098.

WIELAND, B.W., MCKINNEY, C.J., COLEMAN, R.E., “A tandem target system using <sup>16</sup>O(p,pn)<sup>15</sup>O and <sup>16</sup>O(p,α)<sup>13</sup>N on natural water”, *Proc. 6th Int. Workshop on Targetry and Target Chemistry (WTTC), Vancouver* (1995) 173–179.

### **<sup>15</sup>N gas <sup>15</sup>O, <sup>14</sup>N gas <sup>15</sup>O**

BEAVER, J.E., FINN, R.D., HUPF, H.B., A new method for the production of high concentration oxygen-15 labelled carbon dioxide with protons, *Appl. Radiat. Isotopes* **27** (1976) 195–197.

DEL FIORE, G., DEPRESSEUX, J.C., BARTSCH, P., QUAGLIA, L., PETERS, J.M., Production of oxygen-15, nitrogen-13 and carbon-11 and of their low molecular weight derivatives for biomedical applications, *Appl. Radiat. Isotopes* **30** (1979) 543–549.

HARPER, P.V., WICKLAND, T., Oxygen-15 labelled water for continuous intravenous administration, *J. Labelled Compd. Rad.* **18** (1981) 186.

RETZ-SCHMIDT, T., WEIL, J.L., Excitation curves and angular distributions for <sup>14</sup>N(d,n)<sup>15</sup>O, *Phys. Rev.* **119** (1960) 1079–1084.

SAJJAD, M., LAMBRECHT, R.M., WOLF, A.P., Cyclotron isotopes and radiopharmaceuticals XXXIV: excitation function for the <sup>15</sup>N(p,n)<sup>15</sup>O reaction, *Radiochim. Acta* **36** (1984) 159–162.

STRIJCKMANS, K., VANDECASTEELE, C., SAMBRE, J., Production and quality control of <sup>15</sup>O<sub>2</sub> and C<sup>15</sup>O<sub>2</sub> for medical use, *Appl. Radiat. Isotopes* **36** (1985) 279–283.

TAKÁCS, S., TÁRKÁNYI, F., HERMANNE, A., PAVIOTTI DE CORCUERA, R., Validation and upgrading of the recommended cross section data of charged particle reactions used for production of PET radioisotopes, *Nucl. Instrum. Meth. B* **211** 2 (2003) 169–189.

VAN NAEMAN, J., MONCLUS, M., DAMHAUT, P., LUXEN, A., GOLDMAN, S., Production, automatic delivery and bolus injection of [<sup>15</sup>O]water for positron emission tomography studies, *Nucl. Med. Biol.* **23** (1996) 413–416.

VERA-RUIZ, H., WOLF, A.P., Direct synthesis of oxygen-15 labelled water of high specific activity, *J. Labelled Compd. Rad.* **15** (1978) 186–189.

VERA-RUIZ, H., WOLF, A.P., Excitation function of  $^{15}\text{O}$  production via the  $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$  reaction, *Radiochim. Acta* **24** (1977) 65–67.

VOTAW, J.R., SATTER, M.R., SUNDERLAND, J.J., MARTIN, C.C., NICKLES, R.J., The Edison lamp: O-15 carbon monoxide production in the target, *J. Labelled Compd. Rad.* **23** (1986) 1211–1213.

WIELAND, B.W., SCHMIDT, D.G., BIDA, G., RUTH, T.J., HENDRY, G.O., Efficient, economical production of oxygen-15 labelled tracers with low energy protons, *J. Labelled Compd. Rad.* **23** (1986) 1214–1216.

### $^{124}\text{X}$ gas $^{123}\text{I}$

ADILBISH, M., et al.,  $^{123}\text{I}$  production from radioxenon formed in spallation reactions by 660 MeV protons for medical research, *Appl. Radiat. Isotopes* **31** (1980) 163–167.

FIROUZBAKHT, M.L., SCHLYER, D.J., WOLF, A.P., “A solid xenon ice target for the production of I-123”, *Proc. IXth Int. Symp. on Radiopharmaceutical Chemistry, Paris* (1992).

FIROUZBAKHT, M.L., SCHLYER, D.J., WOLF, A.P., Effect of foil material on the apparent yield of the  $^{124}\text{Xe}(\text{p},\text{x})^{123}\text{I}$  reaction, *Appl. Radiat. Isotopes* **43** (1992) 741–745.

FIROUZBAKHT, M.L., SCHLYER, D.J., WOLF, A.P., “‘Failsafe’ gas target for the production of I-123 from Xe-124”, *Proc. 6th Int. Workshop on Targetry and Target Chemistry (WTTTC), Vancouver* (1995) 79–81.

FIROUZBAKHT, M.L., SCHLYER, D.J., WOLF, A.P., Production of iodine-123 from xenon-124: cross-sections and yields, *Radiochim. Acta* **56** (1992) 167–171.

FIROUZBAKHT, M.L., TENG, R.R., SCHLYER, D.J., WOLF, A.P., Production of high purity iodine-123 from xenon-124 at energies between 15 and 34 MeV, *Radiochim. Acta* **41** (1987) 1–4.

GRAHAM, D., TREVENA, I.C., WEBSTER, B., WILLIAMS, D., Production of high purity iodine-123 using xenon-124, *J. Nucl. Med.* **26** (1985) 105.

JUNGERMAN, J.A., LAGUNAS-SOLAR, M.C., Cyclotron production of high purity iodine-123 for medical applications, *J. Radioanal. Chem.* **65** (1981) 31–45.

KURENKOV, N.V., MALININ, A.B., SEBYAKIN, A.A., VENIKOV, N.I., Excitation functions of proton-induced nuclear reactions on  $^{124}\text{Xe}$ : production of  $^{123}\text{I}$ , *J. Radioanal. Nucl. Ch. Le.* **135** (1989) 39–50.

QAIM, S.M., Target development for medical radioisotope production at a cyclotron, Nucl. Instrum. Meth. A **282** (1989) 289–295.

TÁRKÁNYI, F., et al., Excitation functions of (p,2n) and (p,pn) reactions and differential and integral yields of  $^{123}\text{I}$  in proton induced nuclear reactions on highly enriched  $^{124}\text{Xe}$ , Appl. Radiat. Isotopes **42** (1991) 221–228.

WITSENBOER, A.J., DE GOEIJ, J.J.M., REIFFERS, S., “Production of iodine-123 via proton irradiation of 99.8% enriched xenon-124”, Proc. 6th Int. Symposium of Radiopharmaceutical Chemistry, Boston (1986) 259.

ZAITSEVA, N.G., et al., Cross sections for the 100 MeV proton-induced nuclear reactions and yields of some radionuclides used in nuclear medicine, Radiochim. Acta **54** (1991) 57–72.

### **$^{82}\text{Kr}$ gas $^{81}\text{Rb}$**

CHILDS, P.O., et al., Rb-81-(Kr-81)m generators — cyclotron production, dispensing, quantitative measurements and supply, Clin. Phys. Physiol. M. **4** 1 (1983) 97–97.

GINDLER, J.E., OSELKA, M.C., FRIEDMAN, A.M., MAYRON, L.W., KAPLAN, E., Gas target assembly for production of high-purity, high specific activity Rb-81, Appl. Radiat. Isotopes **27** (1976) 330–332.

HELUS, F., GASPER, H., ZEISLER, S., MAIERBORST, W., An automated microprocessor controlled system for the production of a new type of Rb-81/Kr-81m generator, J. Radioan. Nucl. Ch. **140** (1990) 111–119.

HICHTWA, R.D., DAUBE, M.E., NICKLES, R.J., Small-scale targetry for the production of Rb-81 and Mn-51, J. Labelled Compd. Rad. **18** (1981) 227–228.

KOVÁCS, Z., TÁRKÁNYI, F., QAIM, S.M., STÖCKLIN, G., Excitation functions for the formation of some radioisotopes of rubidium in proton induced nuclear reactions on  $^{nat}\text{Kr}$ ,  $^{82}\text{Kr}$  and  $^{83}\text{Kr}$  with special reference to the production of  $^{81}\text{Rb}$  ( $^{81m}\text{Kr}$ ) generator radionuclide, Appl. Radiat. Isotopes **42** (1991) 329.

LAMBRECHT, R.M., GALLAGHER, B.M., WOLF, A.P., BENNETT, G.W., Cyclotron isotopes and radiopharmaceuticals — XXIX:  $^{81,82m}\text{Rb}$  for positron emission tomography, Appl. Radiat. Isotopes **31** (1980) 343.

LAMBRECHT, R.M., SAJJAD, M., Cyclotron isotopes and radiopharmaceuticals — XXXIX: aluminium and nickel targets for Rb-81 production, Appl. Radiat. Isotopes **39** 10 (1988) 1081–1083.

LESSING, G., TÁRKÁNYI, F., QAIM, S.M., Production of  $^{82m}\text{Rb}$  via the  $^{82}\text{Kr}(p,n)$ -process on highly enriched  $^{82}\text{Kr}$ : a remotely controlled compact system for irradiation, safe handling and recovery of the target gas and isolation of the radioactive product, *Appl. Radiat. Isotopes* **48** (1997) 37–43.

RUTH, T.J., LAMBRECHT, R.M., WOLF, A.P., THAKUR, M.L., Cyclotron isotopes and radiopharmaceuticals — XXX: aspects of production, elution and automation of Rb-81/Kr-81 generators, *Appl. Radiat. Isotopes* **31** (1980) 51–59.

SOLIN, O., HESELIUS, S.J., LINDBLOM, P., MANNGARD, P., Production of Rb-81 from Kr – a target study, *J. Labelled Compd. Rad.* **21** (1984) 1275–1277.

STEYN, G.F., MILLS, S.J., NORTIER, F.M., HAASBROEK, F.J., Integral excitation-functions for Kr-nat + p up to 116 MeV and optimization of the production of Rb-81 for Kr-81m generators, *Appl. Radiat. Isotopes* **42** (1991) 361–370.

VANDECASTEELE, C., GOETHALS, P., SAMBRE, J., SLEGGERS, G., Routine production of Rb-81-Kr-81m generators using the Kr-82(p,2n)Rb-81 reaction, *Radiochem. Radioa. Let.* **46** (1981) 285–290.

WATERS, S.L., et al., Production of Rb-81 using a 60 MeV proton-beam - target development and aspects of recovery, *J. Labelled Compd. Rad.* **23** (1986) 1338–1340.

## ABBREVIATIONS

CCD	charge coupled device
CT	computed tomography
EDM	electric discharge machining
EOB	end of bombardment
FDG	2-[ <sup>18</sup> F]-fluoro-2-deoxy-D-glucose
FID	flame ionization detection
GC	gas chromatography
GMP	good manufacturing practices
HID	helium ionization detection
HPLC	high pressure liquid chromatography
MS	mass spectrometry
NIST	National Institute of Standards and Technology
PET	positron emission tomography
QMA	quaternary methyl ammonium
SA	specific activity
SPECT	single photon emission computed tomography
SRIM	The Stopping and Range of Ions in Matter
TCD	thermal conductivity detection
TE	trapping efficiency
UV	ultraviolet



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