# Cyclotron Produced Radionuclides: Principles and Practice

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# Cyclotron Produced Isotopes: Principles and Practice

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# FOREWORD

Application of radioisotopes has shown a significant growth in the last decade and one of the major factors contributing towards this increased growth is the availability of a large number of cyclotrons exclusively dedicated to the production of radioisotopes for medical applications. As per a recent IAEA survey, it is estimated that there are more than 350 cyclotrons available in the Member States (MS) [Directory of Cyclotrons Used for Radionuclide Production in Member States, IAEA-DCRP/2006]. Many of these cyclotrons are dedicated to the production of isotopes for positron emission tomography (PET) more specifically, fluorine-18 for the production of $^{18}$F-FDG (fluorodeoxyglucose). Although production of isotopes other than $^{18}$F using those cyclotrons is limited, their use could be augmented for the production of a large number of isotopes useful in medicine and industry.

The IAEA has been extending support in various forms to MS to acquire as well as enhance the technology for production of isotopes using cyclotrons. Publication of documents covering different aspects on radioisotope production using cyclotrons is one such support identified by MS needing IAEA input. A Consultants' meeting organized during 2004 identified the necessity of documents on different aspects of cyclotron-produced isotopes.

During the preparation of the above document as well as during the deliberations in the 'International Symposium on Trends in Radiopharmaceuticals-ISTR 2005' held in Vienna during November 2005, the need for a comprehensive book on cyclotron with special emphasis on production of isotopes was identified. The main reason for such a request was due to the lack of a single source of up to date information on this topic, despite the availability of a large number of related publications in the scientific literature. Work towards the preparation of such a document was initiated during a Consultants meeting held in Vienna during April 2006. The consultants suggested that the book should incorporate the basic science behind the accelerator technology in addition to giving all relevant information regarding radioisotope production. Consequently this publication contains chapters on accelerator technology, theoretical considerations of nuclear reactions, technology behind targetry, techniques on preparation of targets, irradiation of targets under high beam currents, target processing, target recovery etc. Chapters highlighting the uses of cyclotron-produced isotopes, as well as future directions in this field are included. The targeted readers of this publication are scientists interested in translating this technology to practice, technologists already working in Member States with cyclotrons wanting 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 degrees in related fields will also greatly benefit from this document.

The manuscript for this publication was prepared by the Consultants, Dr. David Schlyer, Brookhaven National Laboratory, USA; Dr. Pierre Van den Winkel, VUB Cyclotron Laboratory, Belgium; Dr. Thomas Ruth, TRIUMF, Canada; and Dr. Manhar M. Vora, King Faisal Specialist Hospital and Research Centre, Kingdom of Saudi Arabia. The IAEA thanks all the Consultants for their valuable contributions. IAEA also thanks those scientists who reviewed the documents. The IAEA officers responsible for this publication are M.R.A. Pillai and M.Haji-Saeid of the Division of Physical and Chemical Sciences.

# CONTENTS

# 1. INTRODUCTION

## 1.1 SCOPE OF THE BOOK

The building of the cyclotron in the thirties of the last century ushered in the beginning of the production of radioisotopes and their subsequent use in medicine, industry, agriculture, and research. With the high energy charged particles and the high beam current available in the cyclotron, it is possible to produce abundant quantities of a wide variety of radioisotopes.

Immediately after World War II, almost all radioisotopes in use were made in a reactor. The production of radioisotopes in cyclotrons for medical applications revived in the 1950's, thanks to the discovery that $^{201}$Tl could be used as an ideal tracer for detecting myocardial perfusion. Thallous chloride labeled with $^{201}$Tl remains the gold standard for measuring cardiac blood flow despite the availability of $^{99m}$Tc myocardial perfusion agents. The preparation of $^{18}$FDG in the mid 1970's and its use for studying glucose metabolism was a major breakthrough leading to the development of the now widely used imaging modality called Positron Emission Tomography (PET). $^{18}$FDG when used along with the PET camera yields excellent quality images of the brain (for studying functional abnormalities), heart (for studying viability function), and tumor (for detection of metastasis). A large number of other $^{18}$F and $^{11}$C labeled radiopharmaceuticals were developed subsequently and the quest for newer and more effective ones continues today.

Apart from the PET and Single Proton Emission Tomography (SPECT) isotopes for diagnostic imaging studies, cyclotron produced isotopes are also finding extensive therapeutic applications. An example is the use of cyclotrons with large beam currents for the production of $^{103}$Pd for brachytherapy applications. Another example of the cyclotron-produced isotopes being used for treatment is the production of alpha particle emitting isotopes, notably $^{211}$At and $^{213}$Bi, for targeted therapy of cancer.

The applications of cyclotron produced isotopes have been expanding at a much faster pace in the last 15 years as seen by the large number of new machines being installed for isotope production. Some cyclotrons are dedicated to the production of a single isotope such as $^{18}$F or $^{103}$Pd. The IAEA has published a directory on cyclotrons used for isotope production in 1998, and a revised version of it was published in 2005 (IAEA-DCR/CD) that documents the cyclotrons available in the Member States.

The present document is aimed at providing information on the various aspects of the production of radioisotopes by using cyclotrons and gives some collective experience on the installation and operation of radioisotope production facilities. Issues such as principles of operation, description of linacs and cyclotrons, how to choose an accelerator, types of facilities and potential uses, theory of radioisotope production, accelerator targetry, enriched isotopes, and radiochemistry are discussed. The paragraphs below provide an outline of the contents of each chapter. The subheading for each section of this chapter refers to the chapter number in the book. Each subsection describes some of the highlights of that chapter.

## 1.2 USES OF ACCELERATOR PRODUCED RADIOISOTOPES

Chapter 2 describes the basic uses of radioisotopes for medical and non-medical applications. The tracer principle forms the basis for most experiments with radioisotopes, and the concept of the tracer principle and how specific activity relates to this concept are given in detail. Factors influencing specific activity are also provided.

Medical applications represent the vast majority of the uses for radiotracers. A number of examples of how radiotracers are used in clinical medicine as well as in basic research are provided. The use of radioisotopes in industry and other research arenas is growing rapidly. While many of the examples provided represent the use of reactor produced radioisotopes, the source of the radioisotope is not important and the reader is encouraged to find the radioisotope that meets his/her criteria for a particular application. One should keep in mind that the half-life should not exceed that required to gain the desired information.

There is also an extensive use of radionuclides in basic chemical and biological research. Using the radioactive atoms as a tracer to determine where atoms migrate during chemical reactions and biological pathways is a common and very useful method of investigation.

## 1.3 DESCRIPTION OF ACCELERATORS

Chapter 3 gives a description of how cyclotrons and linear accelerators work, and the important characteristics of these accelerators for the production of radioisotopes. A general description of the operating characteristics of linacs is provided along with the basic equations which govern the energy of the acceleration. A description of the commercially available linacs is included as of the publication date of this book.

Next, a general description of the operating characteristics of cyclotrons and the basic equations which govern the energy of the accelerator are explained. Included are descriptions of the basic components of the cyclotron such as the RF system, the ion source, the vacuum system, and the extraction system. A description of the commercially available cyclotrons is included as of the publication date of this book and a table of the operating characteristics of these cyclotrons. A brief description of other accelerators that have been used for the production of radioisotopes is given as well.

Choosing an accelerator can be a daunting task. Thus, a brief outline of issues that should be considered is given. While this is not an exhaustive exploration of this complex topic, the issues described will help the user understand the variety of problems and identify which ones are of utmost importance in their circumstances.

The details of the characteristics of commercial cyclotrons designed for radionuclide production are compiled and are given at the end of the chapter. The purpose of these tables is to give people a place to start asking questions concerning the characteristics of the cyclotron, and how one cyclotron would be preferable to another for a particular application.

## 1.4 THEORY OF RADIOISOTOPE PRODUCTION

Chapter 4 presents some basic understanding of the nuclear processes which occur in the transmutation of one element to another. There are a wide variety of nuclear reactions which are used in an accelerator to produce the artificial radioactivity. The bombarding particles are usually protons, deuterons, or helium particles. The energies used range from a few MeV to hundreds of MeV. This chapter explains the compound nucleus model and gives some common terminology of nuclear reactions. The nuclear reaction cross-section represents the total probability that a compound nucleus will be formed and it will decompose in a particular channel. There is a minimum energy below which a nuclear reaction will not occur, except by tunneling effects. This section describes the energetic of nuclear reactions and explores some aspects of the compound nucleus model.

The production rate of a radionuclide is described, including the calculation of the thick target yield and how to obtain and use literature cross-section data.

References to the SRIM code for estimating energy loss in compounds based in the elemental composition are also given. The concept of the saturation factor is described and why it usually takes a long time to produce long-lived radionuclides.

## 1.5 TARGETRY

Chapter 5 provides a brief description of the phenomena associated with accelerator targets and some basic understanding of the practical considerations in the use of cyclotron targets. All cyclotron targets share many characteristics in the basic physics, chemistry, and engineering which go into the design of a target. The problems in the design and construction of cyclotron targets need to be defined. Some practical examples from the literature on how people have arrived at the, sometimes, mutually exclusive solutions to the numerous problems encountered in the optimal design of a cyclotron target are included. An attempt has also been made to present some simple formulas and "rules of thumb" which may be used in the design of cyclotron targetry. In this vein, simple equations have been used and the reader may decide if simple approximations are sufficiently accurate in the particular application under consideration.

In addition to the basic principles, there are practical topics related to the transport of the beam from the accelerator to the target, as well as the important matter of dealing with enriched target material and the ensuing recycling concerns.

## 1.6 TARGET PREPARATION AND IRRADIATION

Chapter 6 explains how cyclotron targets are prepared and irradiated. There is some information on how targets should be manufactured in order to maintain high specific activity for certain radioisotopes. The transport of materials from the target to the hot cell is also covered. The cleaning and routine maintenance of gas and liquid targets is discussed along with some polishing techniques for target surfaces. There is significant section on the preparation of solid targets by electro-deposition. A specific example using $^{201}$Tl is provided. Practical information such as spreadsheets for planning the plating of targets is also given. The issues associated with irradiating targets such as cooling and dealing with beam density and distribution are discussed.

## 1.7 TARGET PROCESSING AND MATERIAL RECOVERY

Chapter 7 deals with the processing of targets including solid, gas, and liquid varieties. Picking up on the $^{201}$Tl example from Chapter 6, we explain how to process this target and recover the enriched material and the necessity of following QC procedures. Two different techniques for the recovery of the enriched target material are described. Examples of $^{11}$C and $^{18}$F precursors are included as examples of radioisotopes produced in gas and liquid targets.

## 1.8 FUTURE DIRECTIONS

Chapter 8 describes some possible trends for the future of radioisotope production. In this chapter the growth of the field is discussed as well as what are seen as the real needs from the community and the IAEA for the future.

# 2 USES OF ACCELERATOR PRODUCED RADIOISOTOPES

## 2.1 INTRODUCTION

The development of nuclear technology is one of the most significant achievements of the 20th century. Today nuclear technology is used in nearly every field and aspect of our lives from medicine, to manufacturing and construction, to powering common household items, to producing electricity for over 16% of the world. A list of some of these common uses may be found at the end of the Chapter.

George de Hevesy made the first practical application of a radioisotope in 1911. At the time de Hevesy was a young Hungarian student working in Manchester with naturally radioactive materials. Not having much money, he lived in boardinghouse and took his meals there with his fellow boarders. He began to suspect that some of the meals might be made from leftovers from the preceding days or even weeks, but he could never be sure. To try and confirm his suspicions, de Hevesy put a small amount of radioactive material into the remains of a meal. Several days later when the same dish was served again he used a simple radiation detection instrument (a gold leaf electroscope) to check if the food was radioactive. It was, and de Hevesy's suspicions were confirmed.

The use of radionuclides in the physical and biological sciences can be broken down into three general categories; imaging, radiotherapy, and radiotracers. Imaging can be further divided into Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT). These topics are beyond the scope of this chapter and will only be described briefly here. All of these uses rely on the fact that the radionuclides are used at tracer concentration. In order to be used as tracers, the radionuclides and the compounds to which they are attached must obey the tracer principles, which state that:

- the tracer behaves or interacts with the system to be probed in a known, reproducible fashion,
- the tracer does not alter or perturb the system in any measurable fashion, and
- the tracer concentration can be measured.

In internal radiotherapy for treating cancer and other diseases, the second principle is, in a strict sense, broken since the point of delivering the radiotoxic substance is to have the emitted radiation cause damage to the tumor tissues. However, in order for the radiotoxic substance to localize, it must follow the known chemical behavior without perturbing that pathway. The following are some typical radionuclides used in each of the broad categories:

Carbon-11 is a positron emitting radionuclide with a half-life of 20.3 minutes used for PET imaging. It is generally produced as $^{11}CO_2$ which can be converted into a wide variety of labeling agents, such as $^{11}CH_3I$ or $H^{11}CN$. Since almost all biological compounds contain carbon, $^{11}C$ finds wide spread use as a tracer in PET. In fact more than 200 compounds have been labeled with $^{11}C$ [1].

Nitrogen-13, with a half-life of 10 minutes, is also a positron emitting radionuclide. However, in addition to its use as a cardiac blood flow agent (as $^{13}NH_4^+$), it is used in applications other than PET imaging. For example, it is widely used in botany studies to determine the kinetics of nitrogen uptake in a variety of plant systems under a variety of conditions [2, 3].

Iodine-123, with a half-life of 13.1 hours, emits $\gamma$-rays with an energy of 159 keV which is ideally suited with imaging in SPECT cameras which have been optimized for use with $^{99m}Tc$ ($\gamma$-ray energy = 140 keV).

In addition, the ease with which an iodine atom can be inserted into a compound makes $^{123}I$ extremely versatile as a radiotracer in SPECT [4-6].

Rhenium-186 is a $\beta^-$ emitter with a low abundance 140 keV $\gamma$ ray. The 1 MeV $\beta^-$ and its 90-hour half-life make it a promising radiotoxic nuclide for therapy. As a chemical analogue of technetium, rhenium possesses similar chemical properties as $^{99m}$Tc and can be used with some of the same compounds that have been developed for imaging tumors [7, 8].

Most of the radiotracers used in vivo should have relatively short half-lives (less than a few hours to at most a few days). There are definite advantages in using short-lived radionuclides, for example, there is a low radiation dose associated with each study, serial studies are possible (sometimes on the same day for tracers such as $^{11}$C), and the radioactive waste disposal problems are minimized if not eliminated. The disadvantages are the need for an accelerator nearby or within easy shipping distance for the longer lived species (a few hours), and rapid chemical procedures are required, especially for the more complex compound formation.

## 2.2 RADIOISOTOPE/RADIONUCLIDE PRODUCTION

Radionuclide production is indeed true alchemy, which is converting the atoms of one element into those of another. This conversion involves altering the number of protons and/or neutrons in the nucleus (target). If a neutron is added without the emission of particles, then the resulting nuclide will have the same chemical properties as the target nuclide. If, however, the target nucleus is bombarded by a charged particle, for example a proton, the resulting nucleus will usually be that of a different element. The exact type of nuclear reactions a target undergoes depends on a number of the parameters, including the type and energy of the bombarding particle. A more complete description of the process of radionuclide production is given in Chapter 4.

The binding energy of nucleons in the nucleus is of the order of 8 MeV on average. Therefore, if the incoming projectile has more than this amount of energy, the resulting reaction will cause other particles to be ejected from the target nucleus. By carefully selecting the target nucleus, the bombarding particle and its energy, it is possible to produce a specific radionuclide. See Chapter 4.

### 2.2.1 Specific Activity

Specific activity (SA) is a measure of the number of radioactive atoms or molecules as compared to the total number of those atoms or molecules present in the sample. The specific activity is usually expressed in terms of radiation units per mass unit. The traditional units have been Ci/mole (or Ci/g) or fraction thereof (now expressed as GBq/mole). If the only atoms present in the sample are those of the radionuclide, then the sample is referred to as carrier free. For example, a compound labeled with $^{211}$At will be carrier free since there are no stable isotopes of astatine.

However, in most cases there are small quantities of non-radioactive atoms or molecules that have a similar chemical behavior and can act as *pseudo-carrier*. The specific activity of an isotope or radiopharmaceutical is important in determining the chemical/biological effect the substance may have on the system under investigation.

The number N of radioactive atoms in a sample can be calculated from the relationship of radioactivity to quantity expressed as:

$$dN/dt = -\lambda N$$

where dN/dt is the disintegration rate in seconds, $\lambda$ is the decay constant in reciprocal seconds ($\lambda = \ln(2)/t_{½}$).

As an example of specific activity, assume that glucose has been labeled with 10 mCi of $^{11}$C with a half-life of 20.3 minutes (1 mCi is $3.7x10^7$ disintegrations per second or dps). The carrier free specific activity can be calculated from the number of atoms contained in the 10 mCi. The number of atoms will be:

$$^{11}C = N = \frac{\frac{dN}{dt}}{\lambda} = \frac{(10mCi)(3.7x10^{7}\,dps/mCi)}{\frac{\ln(2)}{(20.3\min)(60\sec/\min)}} = 6.5x10^{11}\,atoms$$

using Avogadro's number, the number of moles is then $1.08x10^{-12}$ and the SA = $9.3 \times 10^{9}$ Ci/mol.

If the radionuclide had been $^{14}C$ with its 5715 year half-life and following the same process but using the decay constant ($\lambda = 3.82 \times 10^{-12}\ s^{-1}$) for $^{14}C$, then the specific activity will be 62 Ci/mol. If the radiolabelled glucose had been prepared in a plant, the naturally occurring glucose would have lowered the SA due to the non-radioactive glucose molecules. Therefore, it is easy to see that the short-lived radioisotopes potentially have a much higher specific activity.

The use of nuclear reactors for the production of radioisotopes relies on the fact that during the fission process in a reactor, there are large numbers of neutrons produced and thermalized by the surrounding media. These thermalized neutrons are ideal for initiating (n,γ) reactions. In some reactors, the higher energy neutrons are used to produce radioisotopes via other reactions involving the ejection of a charged particle, for example, (n,p) or (n,α) reactions. The fission process is a source of a number of widely used radioisotopes. For example, $^{90}Sr$, $^{99}Mo$, $^{131}I$ and $^{133}Xe$ are all produced in reactors by fission, and can be separated from the uranium fuel cells or from targets of enriched $^{235}U$ placed in the reactor for radioisotope production directly. The major drawbacks from using fission produced materials are the large quantities of radioactive waste material generated, and the large amounts of radionuclides produced, including other radioisotopes of the desired species. In producing $^{131}I$ from fission, the isotopes $^{127}I$ and $^{129}I$ are also formed, thus reducing the specific activity. A more detailed discussion is beyond the scope of this chapter and the reader is referred to the IAEA Technical Document Manual for Reactor Produced Radioisotopes [9].

It is ironic that the first artificially produced radionuclides were created on Lawrence's cyclotrons in the 1930's [10,11], but it took another 30 years before accelerator produced radionuclides began to play a major role in production of medically important radiopharmaceuticals. The principle advantage of accelerator-produced radioisotopes is the high specific activities that can be obtained through the (p,xn) and (p,α) and other reactions involving charged particles that result in the product being a different element than the target. Another significant advantage is that a smaller amount of radioactive waste is generated from charged particle reactions.

Cyclotrons designed for producing medical radioisotopes were initially capable of accelerating protons, deuterons, $^{3}He^{+2}$ and α-particles (the nucleus of $^{4}He$). However, the principle radioisotopes currently used in medical applications can all be produced by protons. The simplicity of design for proton only cyclotrons has resulted in cyclotrons which are capable of generating two or more simultaneous beams of varying energies and intensities. The modern cyclotron is completely controlled by a computer and can be in continuous operation for many days with only minimal attention.

As shown in Table 1, the PET radionuclides are produced from either proton or deuteron reactions. Since most PET research was performed at major research labs having accelerators capable of proton or deuteron production, these reactions were the standard. However, in the early 80's, small compact proton-only cyclotrons became available and cyclotrons specifically designed for producing PET radionuclides were installed in many hospitals.

The major drawback from these proton only cyclotrons lies in the fact that in some cases an enriched target material must be used for sufficient radionuclide to be generated.

TABLE 1. THE MOST COMMONLY USED POSITRON EMITTERS AND TYPICAL REACTIONS FOR THEIR PRODUCTION

| Radionuclide | t ½ minutes | Decay Mode | Reaction | Energy (MeV) |
|---|---|---|---|---|
| $^{11}$C | 20.3 | $\beta^+$ | $^{14}$N(p,$\alpha$) | 11-17 |
| $^{13}$N | 9.97 | $\beta^+$ | $^{16}$O(p,$\alpha$)<br>$^{13}$C(p,n) | 19<br>11 |
| $^{15}$O | 2.03 | $\beta^+$ | $^{15}$N(p,n)<br>$^{14}$N(d,2n)<br>$^{16}$O(p,pn) | 11<br>6<br>>26 |
| $^{18}$F | 110 | $\beta^+$ | $^{18}$O(p,n)<br>$^{nat}$Ne(d,$\alpha$) | 11-17<br>8-14 |

## 2.3 RADIOACTIVE TRACERS

The term radiotracer refers to a radioactive species that is used to follow (trace) the uptake into or function of an organ system in a living plant or animal or a physical/chemical process. Initially, the radiotracers used were radioactive isotopes of naturally occurring elements or chemical congeners of these elements. Other early uses of simple elements as radiotracers were in the use of radioiodine to monitor iodine uptake in the thyroid and the use of radioactive phosphorous to monitor metabolism.

Radioactive isotopes of the elements of sodium and potassium ($^{24}$Na, $^{42}$K) have been used to measure the sodium and potassium content of the body employing the isotope dilution technique. Analysis by isotope dilution involves adding a known mass and specific activity of a substance to a mixture containing an unknown quantity of the substance and taking an aliquot of the mixture and determining the new specific activity of the substance under investigation. It can be shown that the mass of the substance of interest in the unknown mixture can be expressed as;

$$M = M_1 (SA_1 / SA_2 - 1)$$

Where: M is the mass of the substance in the system under investigation, $SA_1$ and $SA_2$ are the specific activities of the tracer added before and after addition to the system, respectively, and $M_1$ is the mass of the spike added to the system.

As an example, suppose we need to know the amount of copper in a system. A spike of copper containing 10 mg with 1 kBq of $^{64}$Cu is added to 20 mL of the unknown sample. After addition and mixing, a portion of the mixture is isolated and the total amount (mass) of copper and the radioactivity determined. In this example, the analysis yields 10.5 mg and 0.5 kBq, respectively, yielding an $SA_2$ value of 0.048 kBq-mg$^{-1}$. Using the above equation, the amount of copper in the unknown sample is:

$$M = 10\text{mg x } ((0.1 \text{ kBq-mg}^{-1}/0.048 \text{ kBq-mg}^{-1}) - 1) = 21 \text{ mg of copper}$$

This method has a number of applications, especially in tracer elemental analyses in living systems.

Another example of the tracer principle is radioimmunoassay (RIA). All RIA procedures are based on the original observation by Berson and Yalow [12,13] that low concentrations of antibodies to the antigenic hormone, insulin, could be detected by their ability to bind radiolabeled ($^{131}$I) insulin. The general principles of radioimmunoassay are readily summarized in the set of competing reactions. Hormone, labeled with a radioactive atom, binds to specific antibody to form a labeled antigen–antibody complex. Radioimmunoassay exploits the ability of unlabeled hormone in plasma or other solutions to compete with labeled hormone for antibody and thereby to inhibit the binding of labeled hormone. As a result of the competitive inhibition, the amount of labeled hormone which is bound to the antibody decreases as the concentration of unlabeled hormone is increased. A calibration or standard curve is set up with increasing amounts of hormone, and from this curve the amount of hormone in the unknown samples can be calculated. This same principle can be applied in a wide variety of hormones, antigens and other biological compounds. Thus the four basic necessities for a radioimmunoassay system are an antiserum to the compound to be measured, the availability of a radioactively labeled form of the compound, a method whereby antibody-bound tracer can be separated from unbound tracer, and a standard unlabeled material. After an incubation of the three essential components, the antigen-antibody complexes, or bound antigens are separated from the free antigens and the radioactivity of either or both phases is measured.

## 2.4 MEDICAL APPLICATIONS

Nuclear Medicine (NM) makes use of the fact that certain radioisotopes emit gamma rays with sufficient energy that the gamma rays can be detected outside of the body.

If these radioisotopes are attached to biologically active molecules, the resulting compounds are called radiopharmaceuticals. They can either localize in certain body tissues or follow a particular biochemical pathway. The following discussion will concentrate on the uses of radioactive substances for the diagnosis or therapeutic treatment of human pathology.

### 2.4.1 Historical Background

Nuclear medicine has its origins in the pioneering work of the Hungarian physician George de Hevesy, who, in 1924, used radioactive isotopes of lead as tracers in bone studies. Shortly thereafter, R.H. Stevens made intravenous injections of radium chloride to study malignant lymphomas.

However, it was not until the discovery of artificially produced radioactive isotopes that the number of available species suitable for use as tracers began to increase. The invention of the cyclotron by Ernest Lawrence in 1932 made it possible to produce radioactive isotopes of a number of biologically important elements. The use of these artificially produced radiotracers continued with J.G. Hamilton and R. Stone using radioactive sodium clinically in 1937. S. Hertz, A. Roberts and R.D. Evans in 1938 used radioactive iodine in the study of thyroid physiology followed in 1939 by J.H. Lawrence, K.G. Scott and L.W. Tuttle studying leukemia with radioactive phosphorus. By 1940 J. G. Hamilton and M.H. Soley were performing studies in iodine metabolism by the thyroid gland in situ by using radioiodine in normal subjects and in patients with various types of goiters.

The first medical cyclotron was installed in 1941 at Washington University, St Louis where radioactive isotopes of phosphorus, iron, arsenic and sulphur were produced. With the development of the fission process during the Second World War, most radioisotopes of medical interest began to be produced in nuclear reactors. After WWII the wide use of radioactive materials in medicine established the new field of what was then called atomic medicine, and only later became known as nuclear medicine. Radioactive carbon, tritium, iodine, iron, and chromium began to be used more widely in the study of disease processes.

Ben Cassen, in 1951, developed the concept of the rectilinear scanner which opened the way to obtaining in a short amount of time the distribution of radioactivity in a subject [14]. This was followed by production of the first gamma camera by Hal Anger in 1958 [15]. The original design was modified in late 1950's to what is now known as the Anger Scintillation Camera, thus heralding the modern era of gamma cameras whose principles are still in use today.

The $^{99}$Mo/$^{99m}$Tc generator system was developed by the Brookhaven National Laboratory in 1957 [16]. Technetium-99m produced via this generator system has become the most widely used radionuclide in nuclear medicine today, accounting for as much as 85% of all diagnostic procedures.

The modern era of nuclear medicine has become known as molecular medicine since it is now possible to translate advances in molecular biology and biochemistry into an understanding of human physiology, and from there into clinical treatment, and the diagnosis of pathology and anatomical abnormalities. The advent of clinical PET for cancer diagnosis makes use of sophisticated tracers to unravel cancer biology.

### 2.4.2 Radionuclides for Imaging

Nuclear Medicine imaging differs from other radiological imaging in that the radiotracers used in nuclear medicine map out the function of an organ system or metabolic pathway and thus, imaging the concentration of these agents in the body can reveal the integrity of these systems or pathways. This is the basis for the unique information that a nuclear medicine scan described in Table 2 provides for various scanning procedures for the various organ/functional systems of the body.

TABLE 2. TYPICAL RADIOISOTOPES AND THEIR USES FOR IMAGING

| Radioisotope | Half-life | Uses |
|---|---|---|
| Technetium-99m | 6 h derived from $^{99}$Mo parent 66 h | Used to image the skeleton and heart muscle, in particular; but also for brain, thyroid, lungs (perfusion and ventilation), liver, spleen, kidney (structure and filtration rate), gall bladder, bone marrow, salivary and lachrymal glands, heart blood pool, infection and numerous specialized medical studies. |
| Cobalt-57 | 272 d | Used as a marker to estimate organ size and for in-vitro diagnostic kits. |
| Gallium-67 | 78 h | Used for tumor imaging and localization of inflammatory lesions (infections). |
| Indium-111 | 67 h | Used for specialist diagnostic studies; e.g. brain studies, infection, and colon transit studies. |
| Iodine-123 | 13 h | Increasingly used for diagnosis of thyroid function, it is a gamma emitter without the beta radiation of $^{131}$I. |
| Krypton-81m | 13 sec from $^{81}$Rb 4.6 h | $^{81m}$Kr gas can yield functional images of pulmonary ventilation, e.g. in asthmatic patients, and for the early diagnosis of lung diseases and function. |
| Rubidium-82 | 65 h | Convenient PET agent for myocardial perfusion imaging. |
| Strontium-92 | 25 d | Used as the 'parent' in a generator to produce $^{82}$Rb. |
| Thallium-201 | 73 h | Used for diagnosis of coronary artery disease and other heart conditions, such as heart muscle death and for location of low-grade lymphomas. |
| Carbon-11<br>Nitrogen-13<br>Oxygen-15<br>Fluorine-18 | 20.4 m<br>9.97 m<br>2 m<br>110 m | These are positron emitters used in PET for studying brain physiology and pathology, in particular for localizing epileptic focus, and in dementia, psychiatry and neuro-pharmacology studies. They also have a significant role in cardiology. $^{18}$Fin FDG has become very important in detection of cancers and the monitoring of progress in their treatment, using PET. |

While there is a wide range of other radioisotopes that are used in imaging, a relatively small number make up the vast majority of all studies in SPECT and PET imaging. Table 3 lists the most widely used radioisotopes for imaging.

TABLE 3. MOST COMMONLY USED RADIOISOTOPES FOR IMAGING

| SPECT | PET |
|---|---|
| $^{99m}$Tc | $^{11}$C |
| $^{123}$I | $^{18}$F |
| $^{201}$Tl | $^{82}$Rb |
| $^{67}$Ga | $^{13}$N |

Table 4 provides the various low energy production routes along with the half-life of the radioisotopes. Technetium-99m is included since this isotope alone accounts for nearly 85% of all nuclear medicine imaging studies. There have been a number of proposals suggesting that $^{99m}$Tc could be produced at an accelerator. The economics of producing $^{99m}$Tc at an accelerator can never compete with the extremely low costs of producing it in a reactor. While there is concern about the ability to build new reactors and thus jeopardizing the availability of this important isotope, the recent construction of reactors in Canada dedicated to $^{99}$Mo production removes this concern for the present.

Iodine-123 has been of interest for nearly 3 decades because of its unique chemistry that makes it possible to attach this isotope to a wide variety of molecules and the $\gamma$-ray energy (159 keV), which is well matched to SPECT cameras. The ability to produce this isotope in high purity from enriched $^{124}$Xe targets made it possible to ship $^{123}$I over long distances and still have high specific activity $^{123}$I available for labeling. However, the production costs are still very high in comparison to other radioisotopes, which will limit its use for the foreseeable future. While $^{123}$I can be produced for local use via the $^{123}$Te(p,n) or $^{124}$Te(p,2n) reactions, the co-production of $^{124,125}$I limits the product's shelf-life.

TABLE 4. NUCLEAR REACTIONS USED TO PRODUCE SOME COMMONLY USED IMAGING RADIOISOTOPES

| Radionuclide | t ½ | Reaction | Energy (MeV) |
|---|---|---|---|
| $^{99m}$Tc | 6.0 h | $^{100}$Mo (p,2n) | 30 |
| $^{123}$I | 13.1 h | $^{124}$Xe(p,2n)$^{123}$Cs<br>$^{124}$Xe(p,pn)$^{123}$Xe<br>$^{124}$Xe(p,2pn)$^{123}$I<br>$^{123}$Te(p,n)$^{123}$I<br>$^{124}$Te(p,2n)$^{123}$I | 27<br><br><br>15<br>25 |
| $^{201}$Tl | 73.1 h | $^{203}$Tl(p,3n)$^{201}$Pb→ $^{201}$Tl | 29 |
| $^{11}$C | 20.3 m | $^{14}$N(p,$\alpha$)<br>$^{11}$B(p,n) | 11-19<br>10 |
| $^{18}$F | 110 m | $^{18}$O(p,n)<br>$^{20}$Ne(d,$\alpha$)<br>$^{nat}$Ne(p,X) | 15<br>14<br>40 |
| $^{64}$Cu | 12.7 h | $^{64}$Ni(p,n)<br>$^{68}$Zn(p,$\alpha$n)<br>$^{nat}$Zn(d,$\alpha$xn)<br>$^{nat}$Zn(d,2pxn) | 15<br>30<br>19<br>19 |
| $^{124}$I | 4.14 d | $^{124}$Te(p,n)<br>$^{125}$Te(p,2n) | 13<br>25 |

Thallium-201 was developed at Brookhaven National Laboratory (BNL) where it was shown that $^{201}$Tl could be used as an ideal tracer for detecting myocardial perfusion [17]. Thallous chloride labeled with $^{201}$Tl has been used extensively for more than 25 years and remains the gold standard for measuring blood flow. Over this period there have been numerous reports of its demise due to the availability of $^{99m}$Tc labeled alternatives, yet the growth in demand for this isotope is still upwards.

The remaining isotopes listed are used in PET imaging. Carbon-11 is extremely attractive because, in principle, one can replace an existing carbon atom in the molecule of interest with the radioactive isotope. However, because of the short half-life, its availability will be limited to those sites possessing an accelerator or which are in the vicinity of one. The demand for $^{18}$F exceeds its availability. To overcome this shortage, a number of central distribution centers have been placed in large metropolitan areas in North America, Europe, and Asia. Although several nuclear reactions are possible, the (p,n) reaction is the choice for producing large quantities of $^{18}$F. If the availability of $^{18}$F continues to grow, $^{18}$F-labeled compounds may begin to compete with other SPECT agents such as $^{123}$I.

Two other isotopes ($^{124}$I and $^{64}$Cu) are candidates for both PET imaging and radiotherapy. The interest in these two is primarily related to the relatively long half-lives. Such properties would enable studies to be performed where the kinetics are slow and exceed the ability to image with $^{18}$F.

The disadvantages include low production rate ($^{124}$I) and the need for expensive enriched target material ($^{64}$Ni, $^{124}$Te). Results from Washington University in St. Louis have shown that high resolution PET images are possible even with the high-energy $\beta^+$-particles associated with $^{124}$I decay, and other photons in coincidence with the $\beta^+$-decay present in $^{64}$Cu [18, 19].

### 2.4.3 Radionuclides for Therapy

The idea of a radioisotope used in therapy is based on the desire to link a radionuclide which has a high linear energy transfer associated with its decay products, such as Auger electrons, β-particles or α-particles to a biologically active molecule that can be directed to a tumor site. Since the $\beta^-$ emitting radionuclides are neutron rich, they have, in general, been produced in reactors. Table 5 lists some of the radionuclides that have been proposed as possible radiotoxic tracers.

TABLE 5. LISTING OF RADIONUCLIDES THAT HAVE BEEN PROPOSED FOR USE AS POSSIBLE RADIOTOXIC ISOTOPES FOR TREATING CANCER

| | | | | |
|---|---|---|---|---|
| $^{47}$Sc | $^{64}$Cu | $^{67}$Cu | $^{77}$Br | $^{90}$Y |
| $^{105}$Rh | $^{103}$Pd | $^{111}$Ag | $^{124}$I | $^{142}$Pr |
| $^{149}$Pm | $^{153}$Sm | $^{159}$Gd | $^{166}$Ho | $^{177}$Lu |
| $^{186/188}$Re | $^{194}$Ir | $^{199}$Pt | $^{211}$At | $^{213}$Bi |

Most of these radionuclides are produced in a reactor, although a few are best produced via charged particle reactions. Table 6 provides the charged particle nuclear reactions that can be used for selected radiotoxic nuclides.

TABLE 6. CHARGED PARTICLE PRODUCTION ROUTES AND DECAY MODES FOR SELECTED THERAPY ISOTOPES

| Radionuclide | t ½ | Decay Mode | Reaction | Energy (MeV) |
|---|---|---|---|---|
| $^{77}$Br | 2.4d | Auger electrons | $^{75}$As(α,2n)<br>$^{77}$Se(p,n)<br>$^{78}$Se(p,2n)<br>$^{79,81}$Br(p,xn)$^{77}$Kr<br>$^{nat}$Mo(p,spall.) | 27<br>13<br>24<br>45<br>>200 |
| $^{103}$Pd | 17.5d | Auger Electrons | $^{103}$Rh(p,n)<br>$^{nat}$Ag(p,xn) | 19<br>>70 |
| $^{186}$Re | 90.6h | $\beta^-$ | $^{186}$W(p,n)<br>$^{186}$W(d,2n)<br>$^{197}$Au(p,spall.)<br>$^{nat}$Au(p,spall.) | 18<br>20<br>>200<br>>200 |

| | | | | |
|---|---|---|---|---|
| | | | $^{nat}$Ir(p,spall.) | >200 |
| $^{211}$At | 7.2h | α | $^{209}$Bi(α,2n)<br>$^{209}$Bi(7Li,5n)$^{211}$Rn<br>$^{232}$Th(p,spall.)$^{211}$Rn | 28<br>60<br>>200 |

The attractive feature of $^{77}$Br is its chemical versatility in addition to its half-life. Production rates are relatively low and purity may be an issue since $^{76}$Br is often co-produced. The demand for $^{103}$Pd, which is used in treating prostate cancer, is continuing to grow. A large number of low energy (18 MeV) cyclotrons are dedicated solely to the production of this isotope.

Rhenium-186 is attractive for a number of reasons. Besides the decay characteristics, rhenium is in the same chemical family as is technetium, thus much of the chemistry developed for technetium can be applied to rhenium.

The production rates from all of the reactions for this radioisotope listed in Table 6 are very low. Thus, the only practical route to this potentially important isotope is via neutron capture in a reactor. This route results in a very low specific activity product, which severely limits its utility.

And finally, the α-emitting isotopes have been of interest for use in therapy because of the high linear energy transfer (LET) associated with the α-decay. Astatine is of interest because it possesses many properties of halogens and each decay of $^{211}$At has an α-particle associated with it. Because of its short half-life, multiple production sites would be required for practical applications. Thus, the interest in producing its parent radionuclide ($^{211}$Rn, $t_{½}$ = 14.6 h) has been suggested as a way of producing and shipping $^{211}$At to remote sites.

## 2.5 RADIOPHARMACEUTICALS

Radiopharmaceuticals differ in one major aspect from regular pharmaceuticals in that they are given in such small concentrations that they do not elicit any pharmacological response. Therefore, there have been a number of attempts to change the name used to describe these substances, for example radiotracers. Present day radiopharmaceuticals are used for diagnostic purposes in about 95% of the cases and for therapy in the remainder [20-22].

In order for a radiotracer (radiopharmaceutical) to be used safely in humans, it must meet high quality standards that include chemical and radiochemical purity, sterility, and freedom from pyrogenic material.

The ideal diagnostic radiopharmaceutical should:

- be readily available at a low cost,
- be a pure gamma emitter, that is, no particle emission such as α and β. These particles contribute radiation dose to the patient while not providing any diagnostic information,
- have a short effective biological half-life so that it is eliminated from the body as quickly as possible,
- have a high target to non-target ratio so that the resulting image has a high contrast (the object has much more activity than the background), and
- follow or be trapped by the metabolic process of interest.

As in all matters of life, there are no 'ideal' radiopharmaceuticals [23]. Thus, in designing a realistic candidate for radiopharmaceutical, the following factors must be considered:

- develop a radiotracer that binds preferentially to a specific site;
- determine the sensitivity of the radiotracer to a change in biochemistry; and
- find a specific biochemical change as a function of a specific disease that matches that sensitivity.

## 2.6 INDUSTRIAL APPLICATIONS

Applications of the radiotracer technique for industry have taken the form of embedding the tracer into a system, or actually inducing radioactivity in the system by charged particle or neutron activation directly. The references for this section provide examples of how this technique can be applied to a variety of problems. The IAEA publication TRS 423 ‘Radiotracer Applications in Industry — A Guidebook’ provides an excellent overview of recent research in the use of radiotracers in a variety of applications. A few examples are given below.

### 2.6.1 Material Processing and Quality Control

Radioisotopes are used to improve the quality of materials in many different ways. All forms of radioactive emissions (alpha, beta and gamma rays) lose intensity as they travel through matter, the loss in intensity can be used to determine the properties of the material. The thickness and density of a material can be determined easily by the attenuation of the radiation, and flaws or cracks may be easily identified by anomalies in the attenuation. As an example, the 250 keV average beta particle from krypton-85 can be used to measure the thickness of thin layers of plastics very accurately.

Small amounts of a radioactive isotope can be used in a tracer to track down problems in the processing of materials. They make it possible to track leakage from piping systems, monitor the rate of engine wear and corrosion of processing equipment, observe the velocity of materials through pipes and gauge the efficiency of filtration systems. As an example, iridium-192 is used to test the integrity of pipeline welds and aircraft parts.

### 2.6.2 Instruments Using Radioisotopes

Instruments containing radioisotopes are widely used because they make it possible to take measurements without direct physical contact with the substance being measured. For example, level gauges containing radioactive sources are used where heat, pressure or corrosive substances, like molten glass or metal, make it difficult or impossible to use direct contact gauges. Strong gamma sources such as $^{192}$Ir and $^{60}$Co are often used in this way. A series of collimated sources with detectors on the opposite side of a conveyor belt can easily detect the level of a substance on the belt.

### 2.6.3 Consumer Products and Services

Radioactive materials supply necessities and conveniences that virtually everyone depends on. They are:

- Many smoke detectors rely on a tiny radioactive source (usually Am-241) to sound an alarm when smoke is present.
- Computer disks ‘remember’ data better when they are treated with radiation.
- Nonstick pans are treated with radiation to ensure that the coating will stick to the surface.
- Photocopiers use small amounts of radioactive materials to eliminate static and prevent paper from sticking together and jamming the machine.
- Cosmetics, hair products and contact lens solutions are sterilized with radiation to remove irritants and allergens.
- Radioactive materials also are used to sterilize medical bandages and a variety of personal health and hygiene products.

## 2.7 ENVIRONMENTAL/BIOLOGICAL APPLICATIONS

Radioisotopes can be used to help understand chemical and biological processes in the environment and in plants. There are two reasons for this usefulness. Radioisotopes are chemically identical with other isotopes of the same element and will react in the same way in chemical reactions, and for many elements some radioactive isotopes of the element have appropriate half-lives and can be easily detected.

### 2.7.1 Agricultural Applications

There are many applications of radioisotopes in agriculture. Radiation has been used to breed new seed varieties with higher yields, such as the ‘miracle’ rice that has greatly expanded rice production in Asia.

The ionizing radiation from radioisotopes increase the number of variations in plants and, with careful selection, can produce crops that are more drought and disease resistant, as well as crops with increased yield or shorter growing time. This practice has been in place for several decades, and has helped to increase food output.

Radioisotopes are ideally suited as tools for the investigations of fertilizers. Important plant nutrients, such as calcium, phosphorus, iron, potassium, copper, sodium, sulfur, and zinc have radioisotopes with the appropriate half-lives and decay characteristics to be used as tracers. These elements can be incorporated in fertilizers and applied to the soil to determine the effect on plant utilization of fertilizer composition or the method of application. Plant uptake of the activated fertilizer can be readily measured and can be distinguished from uptake of the same compound already present in the soil. Phosphorus-32 as a tracer has a wide application in the field of plant physiology and soil chemistry. Research has also been done on the mechanism of nutrient uptake by using this radioisotope of phosphorus. Using rice as a test crop, studies are being done on the absorption, translocation and distribution of phosphate, carbon and nitrogen with the help of super phosphate, urea and ammonium sulfate labeled with $^{32}P$, $^{14}C$ and $^{15}N$ which were applied both in soils and on leaves as spray.

### 2.7.2 Insect Control

Insects destroy about 10% of the world’s crops. Releasing sterile laboratory-raised insects into the wild can sometimes control these pests. The male insects are made sterile using ionizing radiation (usually $^{60}Co$). Female insects that mate with sterile male insects do not reproduce, and the population can be quickly curbed as a consequence. The technique is considered to be safer and better than conventional chemical insecticides since insects can develop resistance against insecticides, and there can be health concerns about chemically treated crops.

### 2.7.3 Plant Physiology

Probably the most widely used tracer for studies in tracer kinetics in plants is $^{13}N$. In spite of its relatively short half-life (<10 minutes), a wide variety of studies have been undertaken to understand the incorporation of nitrogen into plant systems. The use of $^{11}C$ provides the opportunity of producing more complex molecules as is seen in the medical applications.

### 2.7.4 Water Resources

Adequate water is essential for life. However, in many parts of the world water is scarce and in others it is becoming scarcer. Isotope hydrology using tritium (or other readily soluble radioisotopes) makes accurate tracing of underground water resources possible. These techniques are important analytical tools in the management and conservation of existing water supplies and in the identification of new/renewable sources of water. The results permit planning and sustainable management of these water resources. Neutron probes can measure soil moisture very accurately, enabling better management of land affected by salinity, particularly in respect to irrigation.

For surface waters, radiotracers can give information about leakage through dams and irrigation channels, the dynamics of lakes and reservoirs, flow rates and river discharge rate measurements, and silt sedimentation rates. Many countries have used isotope techniques to investigate their water resources in collaboration with the IAEA.

## 2.8 BASIC CHEMICAL/PHYSICAL SCIENCES

Tracers have long been used to probe the kinetics of chemical reactions. With the high sensitivity associated with radioactive decay, very short life times could be monitored accurately.

One of the major uses of kinetic isotope effects (KIEs) is to help chemists model the transition states of organic reactions so they can understand how and why reactions occur. KIE's are the major tool used in these investigations because they give both qualitative and semi-quantitative information about the structure of the transition state. For instance, a leaving group KIE is used to determine the length of the alpha carbon, leaving group bond in an $SN_2$ transition state:

$$\mathrm{CH_3\text{-}Cl} + \mathrm{C{\equiv}N}^{-} \rightarrow [\,\overset{\delta-}{\mathrm{N}}{\equiv}\mathrm{C}\text{- - -}\mathrm{CH_3}\text{- - -}\overset{\delta-}{\mathrm{Cl}}{}^{\neq}]^{-} \rightarrow \mathrm{CH_3\text{-}C{\equiv}N} + \mathrm{Cl}^{-}$$

The theoretical equation relating transition state structure to the magnitude of the KIE is given by

$$\frac{k_L}{k_H} = \frac{\nu_L^{\mp}}{\nu_H^{\mp}}\left(1 + \sum_i^{3n-6} Gu_i\Delta u_i - \sum_i^{3n-7} Gu_i\Delta u_i^{\mp})\right), \text{ where}$$

$\sum_i^{3n-6} Gu_i\Delta u_i$ represents the vibrational energy in the reactant

$\sum_i^{3n-7} Gu_i\Delta u_i^{\mp}$ represents the vibrational energy in the transition state

As the percent $C_\alpha$-Cl bond rupture in the transition state increases, the vibrational energy of the $C_\alpha$-Cl bond (the $\Sigma Gu_i\Delta u_i^{\neq}$ term) decreases and the chlorine KIE increases. Therefore, one can use the magnitude of the leaving group KIE to estimate the amount of $C_\alpha$-Cl bond rupture in the transition state.

It has been shown that by using artificially manufactured isotopes, it is possible to increase the magnitude of the KIE for a particular element by increasing the mass difference between the isotopes used in the experiment [24]. For example, increasing the mass difference between the carbon isotopes used in measuring a carbon KIE to 3 by using $^{11}C$ and $^{14}C$ increased the magnitude of the KIE by a factor of 4.

## 2.9 SUMMARY

Radioisotopes have very useful properties: radioactive emissions are easily detected and can be tracked until they disappear, leaving no trace. These properties lead to many applications for radioisotopes in the scientific, medical, forensic and industrial fields. Table 7 gives a list of radioisotopes and their varied uses.

TABLE 7. COMMON RADIOISOTOPES AND THEIR USES

| | |
|---|---|
| Americium-241 | Used in many smoke detectors for homes and businesses, to measure levels of toxic lead in dried paint samples, to ensure uniform thickness in rolling processes like steel and paper production, and to help determine where oil wells should be drilled. |
| Cadmium-109 | Used to analyze metal alloys for checking stock and sorting scrap. |
| Calcium-47 | Aid to biomedical researchers studying the cell function and bone formation of mammals. |
| Californium-252 | Used to measure the mineral content of coal ash and to measure the moisture of materials stored in silos. |
| Carbon-11,14 | Used in research to ensure that potential new drugs are metabolized without forming harmful by-products. |
| Cesium-137 | Used to treat cancers; to calibrate the equipment used to measure correct patient dosages of radioactive pharmaceuticals; to measure and control the liquid flow in oil pipelines; to tell researchers whether oil wells are plugged by sand; and to ensure the right fill level for packages of food, drugs and other products. (The products in these packages do not become radioactive.) |
| Chromium-51 | Used in research in red blood cell survival studies. |
| Cobalt-57 | Used in nuclear medicine to help physicians interpret diagnostic scans of patients' organs, and to diagnose pernicious anemia. |
| Cobalt-60 | Used to sterilize surgical instruments; to improve the safety and reliability of industrial fuel oil burners; and to preserve poultry, fruits and spices. |
| Copper-64 | Tracer for blood flow, hypoxia, and cell binding studies as PTSM |
| Copper-67 | When attached to monoclonal antibodies and injected into a cancer patient, helps the antibodies bind to and destroy the tumor. |
| Curium-244 | Used in mining to analyze material excavated from pits and slurries from drilling operations. |
| Fluorine-18 | Used in bological tracer molecules such as FDG and FLT for detection of cancer. |
| Gallium-67 | Gallium Citrate may be useful in demonstrating the presence of several types of malignancies. |
| Iodine-123 | Widely used to diagnose thyroid disorders. |
| Iodine-124 | PET tracer used in the same way as Iodine is used for SPECT |
| Iodine-129 | Used to check some radioactivity counters in *in vitro* diagnostic testing laboratories. |
| Iodine-131 | Used to diagnose and treat thyroid disorders. *(Former U.S. President George H.W. Bush and Mrs. Bush were both successfully treated for Graves' disease, a thyroid disease, with radioactive iodine.)* |
| Iridium-192 | Used to test the integrity of pipeline welds, boilers and aircraft parts. |
| Krypton-85 | Used in indicator lights in appliances like clothes washers and dryers, stereos and coffeemakers; to gauge the thickness of thin plastics, sheet metal, rubber, textiles and paper; and to measure dust and pollutant levels. |
| Nickel-63 | Used to detect explosives and as voltage regulators and current surge protectors in electronic devices. |
| Nitrogen-13 | Used as ammonia for cardiac imaging |
| Phosphorus-32 | Used in molecular biology and genetics research. |
| Plutonium-238 | Has safely powered at least 20 NASA spacecraft since 1972. |
| Promethium-147 | Used in electric blanket thermostats and to gauge the thickness of thin plastics, thin sheet metal, rubber, textiles and paper. |
| Rubidium-82 | Used as a blood flow tracer |
| Selenium-75 | Used in protein studies in life science research. |
| Sodium-24 | Used to locate leaks in industrial pipelines and in oil well studies. |
| Strontium-85 | Used to study bone formation and metabolism. |

| | |
|---|---|
| Strontium-90 | Used in survey meters by schools, the military and emergency management authorities. |
| Technetium-99m | The most widely used radioactive isotope for diagnostic studies in nuclear medicine. Different chemical forms are used for brain, bone, liver, spleen and kidney imaging and also for blood flow studies. |
| Thallium-201 | Used in cardiac stress tests |
| Thallium-204 | Measures the dust and pollutant levels on filter paper and gauges the thickness of plastics, sheet metal, rubber, textiles and paper. |
| Thoriated tungsten | Used in electric arc welding rods in the construction, aircraft, petrochemical and food processing equipment industries. It produces easier starting, greater arc stability and less metal contamination. |
| Thorium-229 | Prolongs the life of fluorescent lights. |
| Thorium-230 | Provides coloring and fluorescence in colored ceramic glazes and glassware. |
| Tritium | Used for life science and drug metabolism studies to ensure the safety of potential new drugs; for self-luminous aircraft and commercial exit signs; for luminous dials, gauges and wristwatches; and to produce luminous paint. |
| Uranium-235 | Used in fuel for nuclear power plants and naval nuclear propulsion. |
| Uranium-238 | Used in dental fixtures like crowns and dentures to provide natural color and brightness |
| Xenon-133 | Used in nuclear medicine for lung ventilation and blood flow studies. |

Material derived form http://www.nei.org and other sources.

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# 3 ACCELERATORS

## 3.1 INTRODUCTION

The production of radionuclides with an accelerator demands that particle beams are delivered with two specific characteristics. The beam must have sufficient energy to bring about the required nuclear reactions, and sufficient beam current to give practical yields. This chapter describes the various types of accelerators, their characteristics, and the basic operation in relation to isotope production.

The transformation of one element into another was first demonstrated by Ernest Rutherford in 1919 [1] when he directed the $\alpha$-particles emanating from a sample of polonium onto nitrogen gas and detected the protons being emitted. The future of accelerator production of radioisotopes reached a turning point with the construction of the cyclotron by Ernest Lawrence in 1931 [2,3]. With the cyclotron, it became possible to produce radioactive isotopes of a wide variety for the first time. Researchers from all over the world came to Berkeley to use the artificially produced radiotracers such as radioactive sodium and iodine in the late 1930's. Cyclotron produced radionuclides for biomedical research were used in the late 1930's for some clinical research and for basic research in biochemistry. In 1936 the University of California officially established the Radiation Laboratory as an independent entity within the Physics Department. The reorganized laboratory was dedicated to nuclear science rather than, as in its first incarnation, to accelerator physics. A center for nuclear medicine already existed at the University of California Hospital in San Francisco, where Hamilton and Robert Stone operated the X ray tube built by Sloan. They were joined by Lawrence's brother John, who had been interested in the biological effects of neutrons during a visit to Berkeley in the summer of 1935. Money for the machine promised by Lawrence in 1936 was raised on the ground of its utility in medicine [4].

Even with this background, in the early years, cyclotrons were mainly used in physics research. Radionuclides for medical applications were a sidelight. The first cyclotron dedicated to medical applications was installed at Washington University, St. Louis in 1941, where radioactive isotopes of phosphorus, iron, arsenic and sulfur were produced. During World War II, a cyclotron in Boston also provided a steady supply of radionuclides for medical purposes. In the mid 1950's a group at Hammersmith in the United Kingdom put into operation a cyclotron wholly dedicated to radionuclide production. The major change occurred in the early and mid 1960’s where the work in hot atom chemistry (e.g. the in situ chemistry of nucleogenic atoms occurring in a target being bombarded) laid the foundation for the synthesis of organic compounds labeled with positron emitters. A 1966 article by TerPogossian and Wagner focused on the use of carbon-11 [5]. As the field of Nuclear Medicine has progressed, the number of available types of particle accelerators with varying characteristics dedicated to radionuclide production for nuclear medicine has also expanded. The major classes of accelerators are the positive and negative ion cyclotrons. More recent innovations include superconducting magnet cyclotrons, small low energy linacs, tandem cascade accelerators and helium particle only linacs. These types of accelerators have not gained wide acceptance mainly as a result of lack of experience in radionuclide production applications. While traditional Van-de-Graaff accelerators have been used for radionuclide production, they probably should not be considered for new installations.

Wolf and colleagues [6-8] have reviewed the application of cyclotrons for the production of radionuclides and suggested that the accelerators can be classified into 4 levels reflecting the particle type and energy of these particles. These are listed in Table 1 (adapted from Wolf [7,8]).

TABLE 1. CLASSIFICATION OF ACCELERATORS

| Classification | Characteristics | Proton Energy | Comments |
|---|---|---|---|
| Level I | single particle, p or d (some dual particle) | 10 MeV | |
| Level II | single or multiple particle, p, d | 20 MeV | ($^3$He, $^4$He - not usually available) |
| Level III | single or multiple particle, p, d | 50 MeV | ($^3$He, $^4$He – may be available) |
| Level IV | usually p only | 70-500 MeV | |

Each class of machines is described in more detail below, followed by a section which will focus on the considerations pertinent to the choice of an accelerator and the placement of the accelerator in a typical operating environment.

## 3.2 DEVELOPMENT OF THE LINEAR ENERGY ACCELERATOR (LINAC)

The concept of the linac arose because there is a practical limit to the energy which can be supplied to a particle between two single electrodes. No matter how well the electrodes are insulated, there will be a discharge of the potential to ground. To overcome this limitation, R. Wideroe devised a system in Germany in the 1930's which would allow the particles to be accelerated in many small steps which will add up to a much greater potential than one giant push.

### 3.2.1. Principle of operation

The principle of acceleration used in all accelerators is the fact that a charged particle has its energy changed when it is acted on by an electric field. In the linac, this change in energy is applied by an alternating potential which must be applied in exactly the proper sequence to keep accelerating the particle. In practice, this is achieved with the use of hollow electrodes called drift tubes, which allow the particle to drift at constant velocity within the tube and then be accelerated between the tubes. The particle is accelerated into the tube by an electric field which is opposite in sign to the charge on the particle. As the particle passes through the hollow tube, the phase of the electric field is changed and at the exit of the tube, the particle is accelerated with a push from the field which now has the same sign as the particle. This is shown in Figure 1.

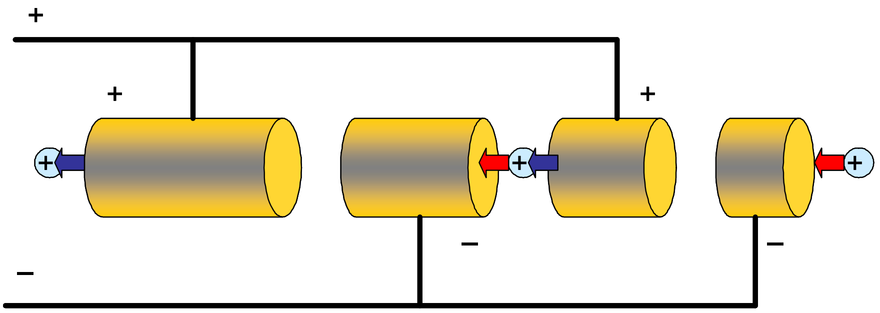

*FIG. 1. Positively charged particles are pulled into the hollow electrode and then pushed out as the phase of the accelerating field is changed.*

One fact which helps to maintain the timing of the acceleration is what is referred to as phase stability. The potential at each stage of the accelerator can be set so that the maximum potential is applied just after the particles have passed a point.

This allows for some margin of error in the timing. If the particle arrives too early, the potential applied will be slightly less than optimum and the particle will traverse the next section more slowly and will be in phase for the next accelerating potential. If the particle is moving too slowly and arrives a little late, the phase of the accelerator can give it a little extra push and again the particle will move to be in phase at the next section of the accelerator. This effect will result in the particles emerging from the end of the linac to be in bunches. The magnitude of this effect can sometimes be a problem in the design of targetry for the linac since the instantaneous power delivered to a target can be quite high.

#### *3.2.1.1. Radio-frequency acceleration*

The radiofrequency (RF) power for the current designs of medical linacs is supplied at high frequency (200-500 MHz) which allows the overall length of the linac to be much shorter. The power for the RF system is usually supplied with a bank of power tubes contained within a coaxial cavity. The use of very high frequencies allows the use of shorter sections for the drift tubes and allows the linac to be shorter. This is an extremely important factor since the particles must traverse the length of one drift tube in one cycle of the RF. This implies that the length of the drift tube must be

$$l = \beta \lambda$$

where $l$ is the length of the tube
$\beta$ is the fraction of the speed of light for the particle
$\lambda$ is the free space wavelength of the radio-frequency

In order to build a linac with reasonable energies and of reasonable size, a high frequency is essential. Power supplies which can provide high power at high frequency have only recently become available.

#### *3.2.1.2. Structure of the Linac*

A linac design which is typical of the new developments incorporates four sections as shown in Figure 2. The first is an ion source which produces a pulsed proton beam of 30 keV with a single electrode system. In the second section, this beam is bunched and then injected into a radiofrequency quadrupole (RFQ) which is the third section. The energy at the end of this section is on the order of 2 MeV. The beam is then transported to the fourth section, where the phase-space of the beam is matched to the phase-space acceptance of the drift tube linac and where the protons are accelerated to the final energy of 11 MeV.

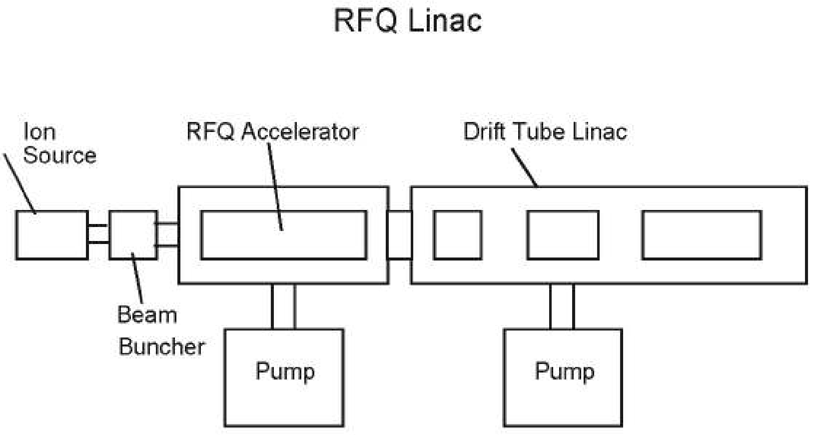

*FIG. 2. Structure of a modern (RFQ) drift tube linac accelerator for production of radionuclides*

### *3.2.1.3. High Vacuum*

In any linear accelerator, a fairly good vacuum must be maintained in order that the charged particles have a mean free path long enough to get from one drift tube to the next without being scattered. In most cases this is done either with a turbomolecular pump, a cryopump or with a diffusion pump. The turbopump and diffusion pumps must be backed with a mechanical pump as is the case with cyclotrons. In linacs, this vacuum must be maintained at the level of better than $1 \times 10^{-6}$ mm of Hg.

### *3.2.1.4. Radiofrequency Quadrupole*

This concept was developed in the Russian Federation but was first applied in the United States of America. The concept is that instead of hollow electrode drift tube, the sections of the acceleration structure are made of vanes which are set at 90 degrees to each other and to the path of the beam. These vanes are charged by the radio-frequency field and serve the same function as the drift tubes of the traditional linac design. The components of a typical linac are shown in Figure 3.

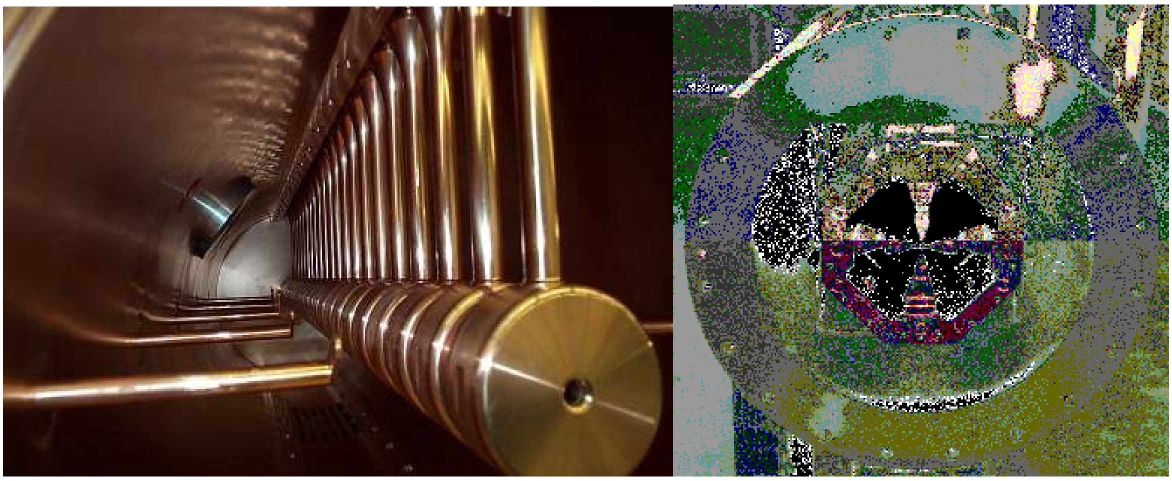

*FIG. 3. Typical Drift tube linac and RFQ. The picture shows the interior of the drift tube linac (left) and the RFQ section (right)*

### 3.2.2 Current Linacs

In the late 1980's the United States Department of Defense supported research and development of new accelerators based on the ‘Star Wars’ technology. There were three funded projects, all of which were of a linear design [9] The aim was to make use of the technology that could produce a very high density of particle beams of low energy. These new accelerators were to compensate for the low production cross-sections at low energy (<10 MeV) with the increased beam current (100 - 1000µA).

While the accelerator technology had advanced to achieve these beam currents, the target technology had not been tried under these severe conditions. Science Applications International Corporation, San Diego, CA USA, planned to build an 8 MeV $^{3}He^{++}$ RFQ accelerator. Its unique features included simplicity in design and operation with low neutron field from the accelerator (no inherent neutrons from the accelerating particle or the nuclear reactions to be utilized - ($^{3}He$,$^{4}He$) and ($^{3}He$,p)). The machine had particle energy of 10 MeV. AccSys Technology Incorporated, Pleasanton, CA USA, proposed a linac, also powered by RFQ, but accelerating protons. A variety of energies could be achieved by varying the length of the accelerator (adding on accelerating cavities). Science Research Laboratory Inc., Somerville, MA, USA, proposed a 3-4 MeV Tandem Cascade Accelerator (TCA) that would accelerate deuterons for $^{15}O$ and $^{13}N$ production and protons for $^{18}F$ production.

The TCA is an electrostatic accelerator that starts with negative ions that pass through a charge stripper to convert to positive ions that doubles the energy for the same potential difference. At the same time Ion Beam Applications, Louvain-la-Neuve, Belgium, built a 3 MeV $D^+$ cyclotron dedicated to the production of $^{15}O$. Several of these small cyclotrons have been situated in Europe. Of the 'Star Wars' machines, only the TCA was built, installed and operated on a routine basis to produce radioisotopes for PET.

## 3.3 DEVELOPMENT OF THE CYCLOTRON

Cyclotrons are the most commonly used devices for the acceleration of particles to energies sufficient for bringing about the required nuclear reactions. It was the remarkable idea of Ernest O. Lawrence to bend the path of the particles in a linear accelerator into a circle and therefore use the same electrode system over and over again to accelerate the particles. This idea is the basis of all modern cyclotrons and has made the cyclotron the most widely used type of particle accelerator. The first model was built in 1930 with proof of particle acceleration being provided by M. S. Livingston in 1931.

Unfortunately, the literature on cyclotrons for medical purposes is somewhat sparse. The book by Livingood published in 1961 [10]) and a more recent review by Scharf [11] are general texts on cyclotrons and other particle accelerators. Detailed information on advances in cyclotrons and other accelerators is available as a series of symposia papers [12]. Cyclotrons for biomedical radionuclide production have been reviewed [8].

### 3.3.1. Principles of Operation

According to the theory of electrodynamics, the rotational frequency of a charged particle traveling in a magnetic field is independent of the radius of its orbit. The energy of the particle increases as the velocity of the particle increases. The cyclotron utilizes this fact to produce particles of reasonably high energy in a relative confined space. The acceleration chamber of the cyclotron is placed between the poles of a homogeneous magnetic field as shown in Figure 4.

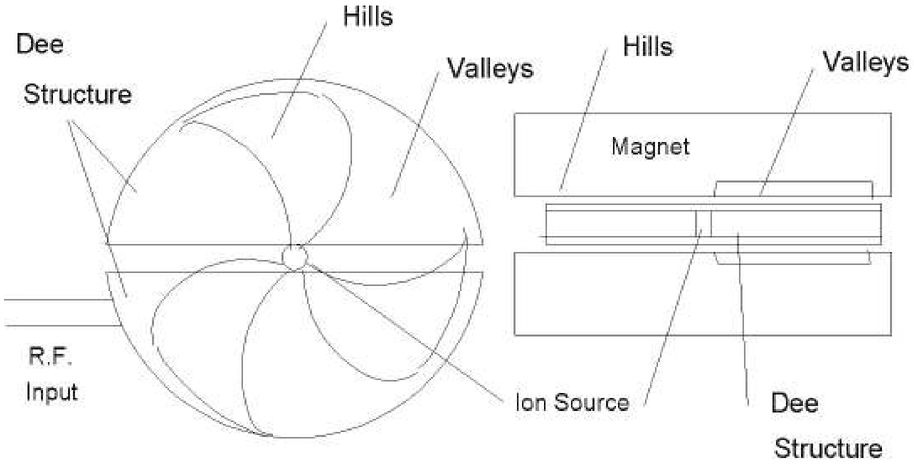

*FIG. 4. Structure of cyclotron showing the magnet, dee structure and ion source*

The magnetic field causes the particles to travel in circular orbits. Ions are produced in an ion source at the center of the machine and accelerated out from the center. The ions are accelerated with a high frequency electric field through two or more hollow electrodes called 'dees'. The ions are accelerated as they pass from one dee to the next through a gap between the dees. Since the rotational frequency of the particles remains constant, as the energy of the particles increases, the diameter of the orbit increases until the particle can be extracted from the outer edge of the machine. The limit on the energy of a particle is determined on a practical basis by the diameter of the magnet pole face. Some very large, high energy cyclotrons have been built, but for the most part, the proton energy is less than about 70 MeV.

#### *3.3.1.1. Radiofrequency Acceleration*

Both the fundamental frequency and higher order harmonics of RF fields may be used for acceleration of charged particles in a cyclotron. The energy of the particle and the harmonic used will determine the exact structure of the hollow electrodes (dees) as shown in Figure 5. When the RF field is coupled to the dees, electric field gradients are produced. In each pair, one of the dees is at a ground potential and the other is at a higher voltage. Since the particle will feel an electric field when entering and leaving a dee, the number of gap crossings per revolution equals twice the number of dees. An accelerating structure may have one, two, three or even more dees. The energy gain of a particle crossing an accelerating gap depends on the charge, amplitude of the potential difference, the phase relationship of the particle to the electric field and the path length between the electrodes.

The particle must cross the gap between two dees at a given time or it will not be accelerated. For a two dee system operating on the fundamental frequency, the time interval is given by the relation

$$1/\omega = r/v$$

where: $\omega$ is the orbital frequency
r is the radius in the median plane
v is the orbital velocity

#### *3.3.1.2. Magnetic Field for Circular Path*

The radius of the orbit of a particle in a magnetic field is given by the relation

$$r = p / [q\ B_z(r)]$$

where r is the radius of the particle in the median plane
p is the momentum of the particle
q is the charge of the particle
$B_z(r)$ is the magnetic induction in the median plane at the radius r

This is the stable equilibrium orbit and particles usually oscillate around this orbit. This equation and the equation for the radius of the particle in the magnetic field are the fundamental equations of cyclotrons. Although in theory the frequency of the orbit is constant, in practice the frequency of the orbit decreases with the radius as a result of relativistic mass increases and the decreasing magnetic field strength with the radius. A particle in phase with the accelerating voltage at the center of the cyclotron will gradually get out of phase and limit the highest energy achievable with this type of cyclotron to about 20 MeV.

The solution to this problem is Azimuthally Varying Field (AVF) cyclotrons which apply the principle of alternating gradient focusing to allow an increase in the magnetic field as the radius increases. The alternating gradient is produced by making the gap between the poles of the magnet smaller or larger.

The areas where there is a smaller gap (stronger field) are called "hills" and those with a larger gap (weaker field) are called "valleys" (Figure 5). The use of spiral, instead of radial hills and valleys, enhances the effect so that cyclotrons of up to 500 MeV may be built. Strong magnetic fields will have an effect on the focusing of the beam and this fringing field must be considered in the design of the cyclotron.

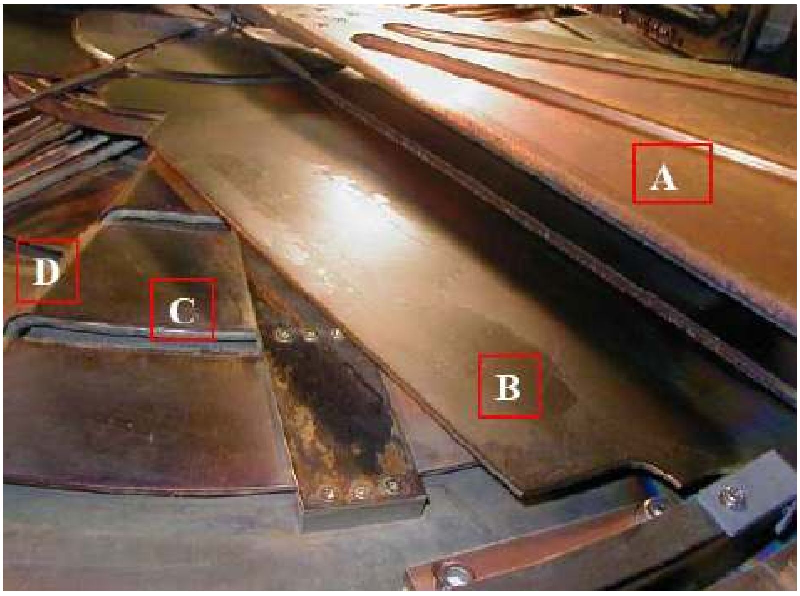

*FIG. 5. Inside cyclotron vacuum tank showing the dees (A), the lower dee cover (B), the circular coils (C) and the transition between the hill and valley (D)*

### *3.3.1.3. Ion Sources*

There are several types of ion sources with different operating characteristics. The extraction of positive and negative ions from the ion source and the path in the central region of the cyclotron are determined in part by the ion source characteristics. Cyclotrons may have either an internal or an external source of ions for acceleration. On most commercial cyclotrons, the source is internal. Charged ions are usually produced by the arc discharge in a gas yielding plasma. The two main types used in cyclotrons are the hot cathode and cold cathode types. In the hot cathode, a heated filament is used to maintain the arc.

In the cold cathode, once the discharge is initiated, no hot filament is used to maintain the plasma during normal operation of the ion source. The spatial distribution and output of an internal source is not well defined. In addition, the ions usually have a broad distribution of energies. These problems are usually overcome by using slits on the ion source which decrease the beam intensity but produce a well defined beam profile. Once the ions are out of the ion source, the path of the beam is further defined with a "puller". This is a small slit in a metal plate which accepts only those ions with the proper energy and position to continue past the first orbit (see Figure 6). The whole assembly is referred to as the central region. Misalignment of the central region results in a beam which is off center. This can usually be detected and corrected with the use of internal probes (to measure beam current) and ion source positioning and intensity adjustments.

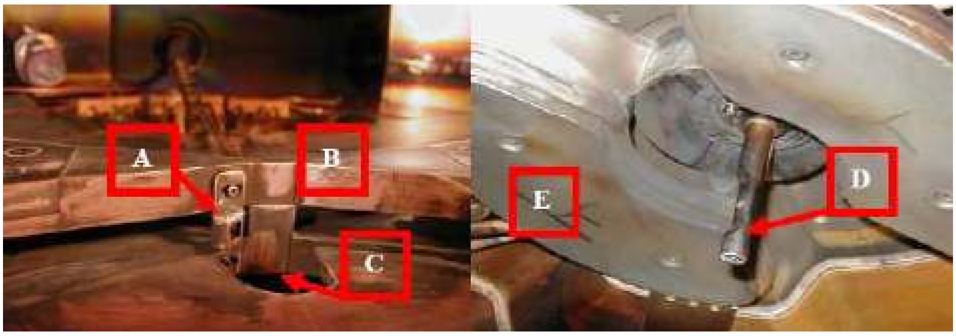

*FIG. 6. Axial ion source configuration showing the puller (A), dee (B), central region where the ion source is lowered into place (C), the ion source cone (D) and the magnetic central region (E)*

#### *3.3.1.4. Vacuum Systems*

The vacuum inside the cyclotron must be maintained at a fairly high level in order that the particles have a mean free path long enough to be accelerated effectively. In the case of cyclotrons, this translates to a pressure inside the tank between 1 x $10^{-5}$ to 1 x $10^{-7}$ mm of Hg, depending on the charge of particle being accelerated, whether the ion source is internal or external, and the type of cyclotron. A higher vacuum ($10^{-6}$ to $10^{-7}$ mm of Hg) is required for negative ion machines than is required for positive ion machines since gas collisions may cause charge stripping.

There are three major types of vacuum systems commonly used for cyclotrons. The first is the oil diffusion pump, the second is the turbomolecular pump and the third is the cryopump. The oil diffusion pump is very reliable and easy to maintain, but has the disadvantage of having oil vapor which can get back into the cyclotron and cause carbon deposits to build up on some surfaces in spite of in-line trapping systems. The usual failure of diffusion pumps is heater burn out. These are easily replaced and the cyclotron can be back on line in a short time. The turbomolecular pumps are much cleaner and have much higher pumping speeds but suffer from the disadvantage of being susceptible to damage to the vanes by a sudden burst of air as would occur in the case of a foil failure on a target.

There are now turbomolecular pumps on the market which are nominally capable of withstanding a sudden burst of gas with no damage. Turbomolecular pumps are also very sensitive to alignment. They must be protected from small pieces of metal which may be in the cyclotron from ruptured foils or flakes. When these pumps fail it is usually necessary to replace the vane assembly which is an expensive and time consuming proposition. Cryopumps are gas entrapment vacuum pumps. The principle of operation is that gaseous substances are bound to the cold surfaces within the pump by means of cryocondensation, cryosorption or cryotrapping. In order to be able to produce a high or ultra high vacuum, the cold surfaces (cryopanels) must be cooled to a sufficiently low temperature. Typical temperatures on the cryopanels are 10 to 20°K. An important aspect in the operation of cryopumps is that of regeneration. Since a cryopump is a gas entrapment pump, the gases which have accumulated in the pump during the ‘pumping’ mode must, from time to time, be removed from the pump. This is done by switching the compressor unit off and by warming up the cryopanels to room temperature or sightly higher so that the released substances can be pumped out by a conventional fore pump. It is often advantageous to have a valve between the cryopump and the vacuum chamber.

#### *3.3.1.5. Extraction Systems*

Extraction of the beam depends on whether the charge on the particle is positive or negative. If the particle is positively charged, the extraction is done electrostatically as shown in Figure 7a. If the particle is negatively charged, the extraction is done by stripping the electrons off the negatively charged ion and allowing the magnetic field to reverse the curvature of the resulting positively charged particles' path and to transport the particles out of the cyclotron as shown in Figure 7b.

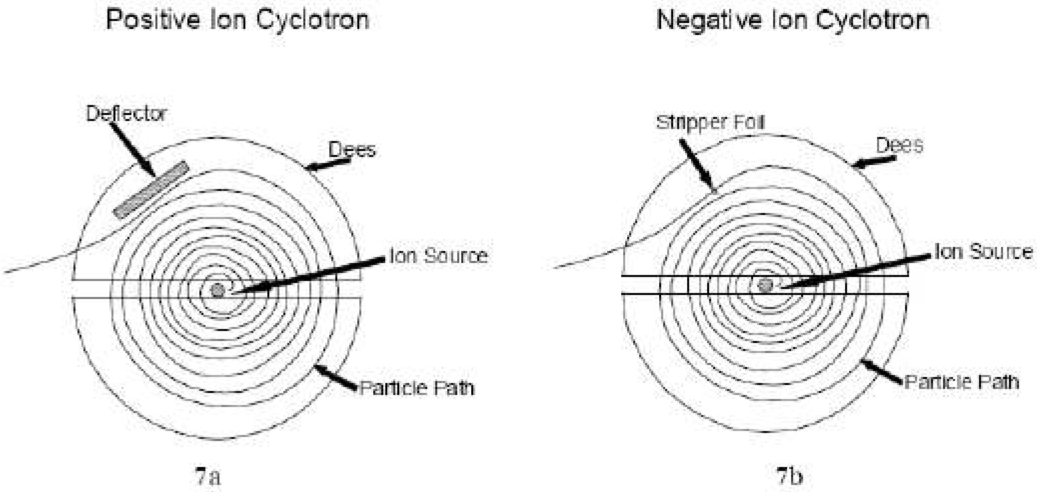

*FIG. 7. Extraction process in modern cyclotrons using either a deflector for positive ions (a) or a stripper foil for a negative ion source (b)*

A picture of the positive ion extraction system showing the septum and deflector is shown in Figure 8. The septum in this case is a split septum. The purpose of the septum is to separate the extracted beam from the circulating beam.

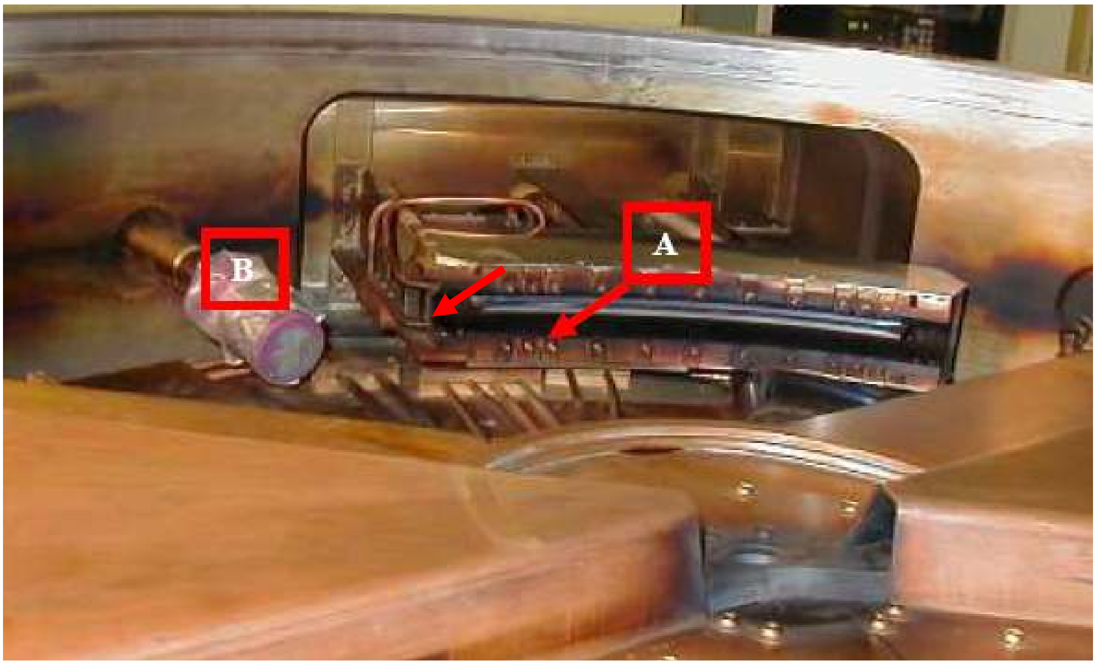

*FIG. 8. Deflector showing the split septum (A), the deflector bar is immediately behind the septum. The picture also shows a beam probe which has been shielded with lead for maintenance operations (B)*

A picture of the negative ion extraction system is shown in Figure 9. The thin carbon foil is used to remove the electrons from the negatively charged ion. This type of foil positioning system can allow extraction of the beam at variable energies.

*FIG. 9. Thin carbon foil and positioning arm in a modern negative ion cyclotron*

### 3.3.2. Current Cyclotrons

The technology of cyclotrons has improved significantly over the last decade. Cyclotrons are now stable machines, run by computer, which can produce a wide variety of radioisotopes. The technology underlying these machines is more complex and a basic understanding of the principles and practical limitations of these machines is very helpful in understanding their problems.

#### *3.3.2.1. Negative and Positive Ion Machines*

Nearly all modern cyclotrons use a negative ion source. Ions are generated by passing the source gas through a plasma maintained in an electric field that generates negative and positive ions (for example, in the case of $H_2$, the primary resulting ions will be $H^+$ or protons, and $H^{=}$ ions, a proton with 2 electrons). The advantage of negative ions resides in the ability to easily have a variable energy cyclotron, to have nearly 100% extraction (see section 3.3.2), and to be able to extract multiple beams simultaneously. Modern ion source technology allows the ion source to reside either inside of the cyclotron where the ions are generated directly in the central region of the cyclotron (internal ion source), or outside of the cyclotron (external ion source) where the ions are injected into the central region for acceleration. There are obviously advantages and disadvantages to each approach. With an external ion source, the vacuum can be operated at very low pressures with very little beam loss due to stripping of the negative ion by the residual gas. However, the vacuum system must be very efficient and clean (no oil contamination) to maintain this high vacuum. With an external ion source, maintenance can be performed without opening the cyclotron or breaking the vacuum. In addition, the center region is not disturbed as in the case of the internal ion source that is part of the center region.

#### *3.3.2.2. Extraction of Beams*

Some early cyclotron designs did not extract the beams of particles and target irradiations were performed by bombarding internal targets. In order to extract the beam, an electrostatic device was inserted at the requisite radius to obtain the desired energy and the beam was deflected out of its normal circular path. The beam was directed by this electrostatic field to a position where there was an exit window in the vacuum tank and the beam impinged on a target attached to the vacuum tank, or was directed to a target station through an evacuated beam line. The relatively poor efficiency of the deflection system meant that as much as 30-40% of the beam was lost through collisions with the deflector or surrounding materials. This loss of beam has two effects, low efficiency in beam production, and activation of cyclotron components due to particle interaction inside the cyclotron tank.

With the negative ion machines, the beam is extracted by passing the negative ions through an ultra thin foil (usually graphite) which strips the loosely bound electrons from the atom resulting in a change in electrical charge of the beam. Thus, the original negatively charged particle ($H^-$) will now be positively charged ($H^+$) and the beam will rotate in the opposite direction. By placing exit ports on the cyclotron tank wall, the beam can be directed out to the appropriate target systems. The variable energy feature is accomplished by moving the extraction foil to different radii. The extraction of multiple beams is accomplished by inserting the extraction foil(s) so that they only intercept part of the beam, allowing the remainder to continue its acceleration to the next extraction foil. Thus, not only two simultaneous beams are possible, but also, beams of different energy and intensity. In general, the extraction arm is calibrated according to position and energy.

#### *3.3.2.3. Energies and Particles*

The energy of the accelerator needed again depends on the demands of the program. As can be seen from Table 2, the range of nuclides produced and the quantities increases with particle energy. This table shows only proton reactions and only a few of the radionuclides which can be produced at these energies.

TABLE 2. LIST OF POPULAR RADIONUCLIDES VERSUS THE PROTON ENERGY REQUIRED FOR PRODUCTION

| Proton Energy (MeV) | Radionuclides easily produced |
|---|---|
| 0-10 | F-18, O-15 |
| 11-16 | C-11, F-18, N-13, O-15, Na-22, V-48 |
| 17-30 | I-124, I-123, Ga-67, In-111, C-11, F-18, N-13, O-15, Na-22, V-48, Tl-201 |
| 30+ | I-124, I-123, Ga-67, In-111, C-11, F-18, N-13, O-15, Sr-82, Ge-68, Na-22, V-48 |

However, this increase in the number of radionuclides which may be produced comes with a price both in the equipment expenses and in the infrastructure. In addition, the number of side channel reactions opens up as the energy increases and unwanted radionuclides can be produced. This is especially true at energies greater than 30 MeV.

The production of the traditional radioisotopes used in Nuclear Medicine ($^{201}$Tl, $^{67}$Ga, $^{123}$I, $^{111}$In) has been via proton reactions for more than 25 years. However, many of the most useful radionuclides can be produced with proton energies of below 30-40 MeV. Higher energy cyclotrons (greater than 40 MeV) are usually installed only at large laboratories, government facilities or large commercial facilities where radionuclides are produced for sale. The particular choice of particle(s) and energy will depend on the envisioned program. The selection of a cyclotron will also depend on which radionuclides are needed to prepare the radiopharmaceuticals used in the clinical and research programs, and whether these radioisotopes will be distributed to other locations.

## 3.4 OTHER ACCELERATORS

### 3.4.1 Tandem Cascade Accelerators

The tandem cascade accelerator uses a single large potential to accelerate a charged particle. This type of accelerator was first developed by R. J. Van de Graaff in 1931. The physical principle underlying the machine is that an electric charge placed within a hollow metal conductor must move to the outside surface of the conductor. The accelerator based on the Van de Graaff principle in use today for PET isotope production is the tandem cascade accelerator [13]. This type of accelerator is composed of four sections. The first is an ion source, the second is an acceleration chamber, the third is a high voltage terminal with a stripper foil, and the fourth is a second acceleration chamber.

A positive charge is accumulated on the high voltage terminal at the center of the acceleration tube assembly. Negatively charged ions are inserted at ground potential from the ion source at one end of the tube. The ions are accelerated from ground potential to a high voltage at the central high voltage terminal. At this point the charge is stripped off the ion by a thin stripper foil and the repulsive forces accelerate the ion to twice the energy of the high voltage terminal. The acceleration assembly is usually insulated from the outside with sulfur hexafluoride gas which is capable of maintaining a high electric field gradient without ionizing. At the end of the second acceleration tube is the target for the production of the radioisotopes.

### 3.4.2 Van de Graaff Accelerators

The most common Van de Graaff accelerator is the self-excited type. A self excited generator refers to what happens when two different materials come together and are then pulled apart. The generator consists of a well rounded high voltage terminal isolated from ground on an insulating column, and a charge conveying system consisting of one or more flat endless belts of insulating material running between this terminal and ground. Electric charge is transported by the belt into the hollow terminal, where it is removed. The maximum voltage which can be maintained on the terminal depends only on its geometry and the dielectric of surrounding insulating medium. The original Van de Graaff generator was designed and built by Dr. Robert J. Van de Graaff (US Patent 1,991,236), around the early 1930's. A diagram is shown in Figure 10.

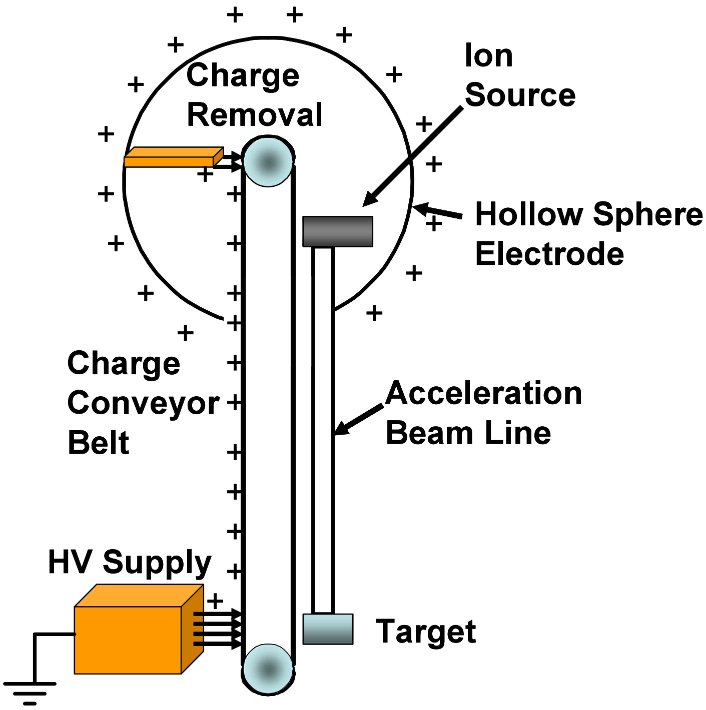

*FIG. 10. Schematic diagram of the Van de Graaf accelerator*

The Pelletron® charging chain used in most modern Van de Graaff accelerators was developed in the mid 1960’s as an improvement over the older charging belts. These belts suffered from a number of operational difficulties including terminal voltage instability and susceptibility to spark damage. Also, they generated belt dust which necessitated frequent cleaning inside the accelerator tank. The chain rapidly proved to be more durable than the old belts, while producing a greater terminal stability than had been possible before. It eliminated the belt dust problem as well.

The chain does not limit ultimate terminal potential, and it is in use in electrostatic accelerators up to and above 25 MV. Today's Van de Graaff accelerator is exploited mainly for physics research and rarely used for radionuclide production.

### 3.4.3 Superconducting Cyclotrons

The basic principles of operation of these machines are the same as those for a conventional cyclotron. Using a superconducting magnet, these cyclotrons can be made very compact but must be maintained at liquid helium temperatures. The weight of the magnet is about 1/5 of the weight of a magnet on a conventional cyclotron. Since the magnet is superconducting, the power requirements are much less. The higher magnetic field causes the orbits to be spaced closer together. The accelerated particle is $H^-$, so the extraction system utilizes a stripper foil.

## 3.5 CHOICE OF AN ACCELERATOR

The question we are left with is 'Which type of accelerator is best for my situation?' There are some practical considerations when making that decision. The main factors are the initial cost, the reliability, the radiological hazards, the operating costs, the installation costs and the available support from the manufacturer. Some of these aspects are outlined in the next sections.

### 3.5.1 Comparison Between Cyclotrons and Other Accelerators

There are several aspects to consider when choosing an accelerator. Some of the characteristics that may be considered are given in Table 3.

TABLE 3. GENERAL CHARACTERISTICS OF ACCELERATORS FOR RADIONUCLIDE PRODUCTION

| Accelerator Type | Advantages | Disadvantages |
|---|---|---|
| Positive Ion Cyclotron | Proven record<br>Versatility<br>Ease of maintenance | High Cost<br>High activation |
| Negative Ion Cyclotron | Extraction efficiency<br>Low activation<br>Beam uniformity | High cost<br>High vacuum requirements<br>Maintenance of stripper foil |
| Superconducting cyclotron | Compact size<br>Low power | Liquid helium maintenance |
| Linac | Stable operation<br>Low power | Targetry<br>Size |
| Tandem cascade | Low power<br>Low cost | Targetry |
| Helium-3 Linac | Low power<br>Stable operation | Low specific activity<br>Targetry |

The first consideration with any accelerator is whether or not it is capable of producing sufficient quantities of radionuclides for particular needs of the facility. Regardless of what type of accelerator is installed, it must be kept in mind that the accelerator delivers protons, deuterons, or less commonly, helium-3 and helium-4 ions. Cross-sections of nuclear reactions for production of most radioisotopes are well characterized, and the practical yields as a function of the particle energy are also well known. The selection of an accelerator is determined in practice by the energy of the particle beam required (see Table 1) for the desired nuclear reaction. For example, a facility wishing to produce only the conventional PET isotopes ($^{11}C$, $^{11}N$, $^{15}O$and $^{18}F$), the Level 1 cyclotron that delivers a 10 MeV proton beam may be sufficient.

On the other hand, a center wishing to manufacture the SPECT isotopes (for example $^{201}Tl$, $^{67}Ga$, $^{123}I$, $^{111}In$, etc.) must consider a cyclotron capable of delivering a higher energy particle beam (Level 2 or Level 3).

Of all the various accelerators, cyclotrons are by far the most extensively used for the production of PET and SPECT radioisotopes. It is therefore to be expected that there is a great deal more information concerning the application and reliability of the cyclotron in comparison to the other types of accelerators. In general, cyclotrons have proven to be reliable accelerators and to provide optimum conditions for consistent isotope production. The linacs and Van de Graaff accelerators have also been used for production of isotopes, but not commonly. Although linacs are also stable machines, they have been used in centers where there are accelerator physicists to address any problems and do not have a history in radioisotope production facilities. As more linacs are placed in radioisotope production centers, however, a better idea can be obtained as to how reliable they will be. The tandem cascade accelerator and the He-3 RFQ are accelerators which were built and tested, but proved to have very limited application in radionuclide production.

### 3.5.2 Radioisotope Yield Considerations

For routine production of radioisotopes, the practical yield can be quite different from the saturation yield of a radionuclide usually found in the literature. Saturation occurs when the production rate of the radionuclide equals the decay rate. For any radionuclide $R = N\lambda/(1-e^{-\lambda t})$, R is the saturation value, N is the number of atoms and $\lambda$ is the decay constant. In a practical sense, this limit is reached at about 5 half lives. For example, the irradiation time for $^{18}F$ production to reach saturation is about 9 hours, which is much longer than one would normally irradiate this type of target. Oxygen-15 production, on the other hand, reaches saturation at about 10-12 minutes which is a more practical irradiation time. Today each manufacturer will present the buyer with a ‘guaranteed’ yield of radionuclide under defined conditions. This is a primary consideration, especially if clinical applications are contemplated.

The chemical form of the radionuclide is also of major interest in considering the attributes of any machine. The target material must withstand the intensely ionizing particle beam and must be able to withstand the intense radiation field accompanying the particle bombardment. The question of chemical form of the radioisotope coming from the target, which target material to use, and the specific bombardment conditions have been a matter of research since the early 1950’s. Target conditions can be manipulated to some extent to provide the desired precursors for syntheses of labeled compounds directly from the target.

Another aspect relating to chemistry is the choice between proton only machines and two particle proton, deuteron machines. If a proton only machine is chosen (Table 1), enriched isotopes are needed to produce some of the four PET radionuclides. If a dual particle machine is chosen, the production of $^{15}O$ and $^{13}N$ can be done with natural abundance target materials. Other radioisotopes may require enriched isotope targets with either protons or deuterons.

### 3.5.3 Characteristics of Commercial Cyclotrons

A table with the characteristics of commercial cyclotrons designed for PET radionuclide production (see Annex 1) and a table with the characteristics of commercially available cyclotrons with energies of 30 MeV or more (see Annex 2) are given. These tables are not complete and are based on the available data in 2005. The entries are the understanding of the authors and should always be verified with the commercial suppliers. The purpose of these tables are to give the basic characteristics of the cyclotron and how one cyclotron would be preferable to another for a particular application. With these characteristics in mind, it should be possible to discuss options with the manufacturers and get the best match between the cyclotron and your particular situation.

There are models and types which have proven to be free from problems while others need constant attention. Sometimes these two extremes are seen in cyclotrons from the same manufacturer and depend entirely on the design of the cyclotron. With the advent of crystal oscillators, computer mapping of magnetic fields, and computer control of source position, arc voltage and so forth, the amount of time spent tuning a cyclotron has been greatly reduced. The best indicator of how a machine will perform is how that machine has performed in the past and the experience of other centers which have that particular machine.

### 3.5.4 Operating Costs

Table 4 is a list of the typical operating expenses for a cyclotron. These include the routine operations and consumable supplies. The exact cost of all these items will depend on the location and the infrastructure of the facility. Some very general estimates are given from experience in the United State of America.

TABLE 4. ESTIMATED OPERATING COSTS OF A CYCLOTRON

| Description | Quantity Per year | Estimated cost US$/year |
|---|---|---|
| Electrical power (cyclotron operations) | 250 MW-hr | 25000* |
| Electrical power (building and air handling) | 100 MW-hr | 10000* |
| Parts and supplies | N/A | 10000 |
| Annual service | 1 | 50000-80000 |

* based on a cost of US$0.10 per kilowatt-hour.

### 3.5.5 Maintenance

Routine maintenance is extremely important for all accelerators. Since the accelerator is often in constant use, some parts tend to wear quickly. Because the power involved in a typical cyclotron is often more than 30 kilowatts, the power delivery chain is an especially vulnerable link in the operation of the cyclotron and requires special attention. O-rings and other seals, especially on moving parts, have a relatively short lifetime and need to be replaced frequently. Vacuum pump maintenance is another key point.

#### *3.5.5.1 Maintenance Schedule*

This is a routine maintenance schedule based on a current cyclotron. The maintenance schedule should be supplied for each cyclotron by the manufacturer. This list is only to give an idea of the tasks involved in maintaining a cyclotron. The routine maintenance tasks have been broken down into three categories related to the difficultly of performing the procedure.

*Level I: Routine Maintenance*

The cyclotron does not have to be shut down to perform Level I maintenance operations. These tasks are performed by trained cyclotron operators.

*Level II: Preventive Routine Maintenance*

These maintenance tasks are to be performed during regularly scheduled maintenance shutdowns of the cyclotron. They should be performed only by on-site service crew. Spare parts required for this maintenance level should be kept on site.

*Level III: Major Repairs and Replacements*

This level includes major repairs and replacements that cannot be performed during a regularly scheduled maintenance shutdown of the cyclotron.

TABLE 5. LEVEL I MAINTENANCE TASKS

| Procedure | Frequency |
|---|---|
| Inspect dry nitrogen gas supply | Before use, as required |
| Inspect helium gas supply | Before use, as required |
| Inspect hydraulic system | Before use |
| Reset fuses and breakers | As required |
| Replace bolus transfer lines | As required |
| Inspect chilled water system | Daily |
| Inspect compressed air system (+ check for water) | Daily |
| Monitor water system | Daily |
| Inspect hydrogen gas supply | Weekly |
| Check and record water resistivity | Every 2 weeks |
| Replace ion exchange column | As required |
| Check hydrogen gas circuit for leaks | Monthly |
| Check and record cryocompressor helium pressure | Monthly |
| Inspect the rough vacuum pump oil level and condition | Monthly |
| Check for water in compressed air water separator | Daily |
| Change water filters | As required (expect 2 to 4 weeks until system is clean) |
| Clean compressed air dust collectors and breathers | Monthly |
| Inspect air hoses | Annually |

TABLE 6. LEVEL II MAINTENANCE TASKS

| Procedure | Frequency |
|---|---|
| Replace O-rings | As required |
| Replace ion source gas bottles (H2 ) | As required |
| Remove water from a cooling circuit | As required |
| Regenerate the ISIS cryopump | Monthly |
| Vacuum leak testing | As required |
| Purge cryopump coldheads | As required |
| Change the ion source filament | As required |
| Clean the roughing network | Every 6 months |
| Regenerate the main tank cryopump | Every tank access |
| Add helium to the cryopump system | As required |
| Clean/replace RF amplifier filter | Every three weeks |
| Clean dust from equipment and filters | Monthly |
| Replace the oil in rough vacuum pump BP | Every 3 months |
| Clean the turbopump backing line | Every BP oil change |
| Change the adsorber in the cryopump compressor | Every 3 years |
| Replace the PLC battery | Annually |
| Replace helium system 7m filter | Annually |
| Replace SMC quick release fittings | Every 2 years |
| Replace BNC bulkhead connectors | Every 2 years |

A cyclotron specialist from the manufacturer must be contacted prior to the work and possibly present when the maintenance and repair tasks at this level are performed. The spare parts required to complete these tasks will be delivered from the manufacturer as required.

The frequency of each maintenance task is summarized in the tables 5-7. The frequency times may vary depending on the intensity of machine operation. The times shown in brackets are for a typical installation.

TABLE 7. LEVEL III MAINTENANCE TASKS

| Procedure | Frequency |
|---|---|
| Clean or change inflector insulators | As required |
| Re-align inflector | As required |
| Replace inflector | As required (~ 5 years) |
| Change the extraction foil | As required (every 20-50 mA hours) |
| Clean or change Einsel Lens Insulators | As required |
| Set water flow in a cooling circuit | As required |
| Repair probes cooling line | As required |
| Repair extraction probe | As required |
| Replace hydraulic cylinder/line | As required |
| Replace He compressor adsorber | Every 3 years |
| Replace an ion source lens or insulator | As required |
| Replace target windows | Every 6 months |
| Repair target selector | As required |
| Repair RF cooling line | As required |
| Replace RF amplifier tube | As required |
| Calibrate the Convectron gauges | Annually |
| Calibrate the cryopump temperature sensors | Annually |

Routine maintenance of the services involves only the few simple tasks described below.

*Hydrogen, Nitrogen, and Helium Supply:*

- Check the pressure in the nitrogen bottle in advance of any venting.
- Check pressure in the hydrogen and deuterium bottles on a regular basis as established by site usage.
- Check the pressure in the helium bottle prior to running beam.

*Replacing Ion Source Gas Bottles*

Ion source gas bottles should be replaced when the bottle pressure is less than 300 psi. The UHP hydrogen and deuterium can have a long delivery.

*Recommended Spare Parts List.*

A list of recommended spare parts that should be obtained from the manufacturer during the commissioning of the cyclotron is given below. The parts list will vary, but a few items will be common to all cyclotrons. These items are listed in Table 8.

TABLE 8. TYPICAL SPARE PARTS INVENTORY

| Item | Quantity |
|---|---|
| Ion source filaments | 10 |
| Final amplifier tube | 1 |
| Driver amplifier (tube or transistors) | 1 each |
| Cryopump | 1 |
| Power supply boards | 1 of each type |
| Diodes | 1 of each type |
| Transistors | General assortment |
| Filters | Assortment |
| Target foils | Assortment |

|  |  |
|---|---|
| Stripper foils | 1 six month supply |

## 3.6 CONCLUSION

This chapter has attempted to give the reader a brief introduction to the various types of accelerators, their characteristics, and practical utility for production of radioisotopes for clinical applications. Comparison of the advantages and disadvantages of each type of accelerator indicates that cyclotrons are by far the preferred type of accelerators for practical production of radioisotopes. Choice of an accelerator depends on the intended radioisotope production objectives of the facility and the location and environment of the accelerator.

There are, however, some key questions to be asked when choosing an accelerator for the production of PET radioisotopes. A short list of these questions is provided below:

i. Will this machine produce the amount of radioisotope necessary for our operation?
ii. Is this machine reliable?
iii. What are the initial costs and how do they compare to the operational costs?
iv. What personnel will be needed to operate and maintain the machine and associated hardware?
v. What will be required to shield this accelerator in our environment?
vi. What are the power and water requirements and are adequate supplies available?
vii. Is help from the manufacturer readily available and how much does it cost?
viii. How will the radiation safety aspects be implemented and documented?
ix. How will radioisotope emissions to the environment be monitored and controlled?
x. Are the target materials (enriched isotopes) required readily available?

This list of questions is a starting point and the answers should be available for all the accelerators under consideration before a final decision is made. The best course is always to arm yourself with as much information as possible.

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# 4 RADIOISOTOPE PRODUCTION

## 4.1 INTRODUCTION

The production of radioisotopes for use in biomedical procedures, such as diagnostic imaging and/or therapeutic treatments, is achieved through nuclear reactions in reactors or from charged particle bombardment in accelerators. In reactors, the nuclear reactions are initiated with neutrons while in accelerators, the typical charged particle reactions utilize protons although deuterons and helium nuclei ($^{3}He^{++}$ and α particles) play a role. While the production of $^{99}Mo$ for the $^{99}Mo/^{99m}Tc$ generator is performed in reactors and the procedures using this generator account for nearly 90% of all Nuclear Medicine procedures, this Chapter will focus on utilizing low energy (<50 MeV protons/20 MeV deuterons) accelerators for the production of radioisotopes.

One clear advantage that accelerators possess is the fact that, in general, the target and product are different chemical elements. This makes it possible to i. find suitable chemical or physical means for separation, ii. obtain high specific activity preparations due to the target and product being different elements, and iii. produce fewer radioisotopic impurities by selecting the energy window for irradiation.

The available accelerators fit into three categories (see Chapter 3). First there are the university-based cyclotrons that are typically multi-particle machines with energies around 30-50 MeV. Second, there are the hospital-based machines, which are generally dedicated to the production of the standard PET radioisotopes ($^{11}C$, $^{13}N$, $^{15}O$, and $^{18}F$). These cyclotrons accelerate protons in the 10-19 MeV range, and some also produce deuterons with an energy of about half that of the proton (5-9 MeV). Third, these are the cyclotrons used by industry for large-scale production that are typically 30 MeV proton- only machines, although some are using lower energies for dedicated production of $^{103}Pd$.

Several national laboratories from around the world are involved in the production of radioisotopes that are not produced by the commercial radioisotope producers. Examples of these are $^{82}Sr$ for $^{82}Sr/^{82}Rb$ generator, $^{68}Ge$ for $^{68}Ge/^{68}Ga$ generator, and PET calibration sources. These machines are typically operated at greater than 100 MeV and accelerate protons with a beam current exceeding 150-200 μA. The limitations of these high-energy facilities include the difficulty associated with scheduling, since most of these facilities are machines that have been built around Nuclear Physics programs with medical applications using the accelerator in parasitic mode, or when the physics program is not operational. Another problem is the range of products produced. Because of the high energy of the proton beam, the dominant reaction mechanism is spallation, which produces not only many different atomic species, but also many isotopes of the same element. These not only produce possible radioactive contaminants, but also stable species that can affect the specific activities of the desired product.

There are three major reasons the accelerator produced radioisotopes are used widely and are becoming ever more popular. These are: i. accelerator produced radioisotopes have more favorable decay characteristics (particle emission, half-life, gamma rays, etc.) in comparison to the reactor produced radioisotopes, ii. the radioisotope cannot usually be produced in a reactor with high specific activity, and iii. perhaps, the most important is that access to a reactor is often very limited. The number of reactors available has become significantly fewer than the number of cyclotrons available to the scientific community. This reduction in the number of available reactors is a problem that was predicted to become more severe over the next decade in 1983 [1]. This prediction has been born out over the last 20 years.

## 4.2 NUCLEAR REACTION MODELS

In the classic sense, a reaction between a charged particle and a nucleus cannot take place if the center of mass energy of the two bodies is less than the coulomb barrier. In the case which applies to the production of radionuclides with a cyclotron, this implies that the charged particle must have the energy greater than:

$$B = Zze^2/R$$

where: Z and z are the atomic numbers of the two species
$e^2$ is the electric charge, squared
R is the separation of the two species in cm.

Actually, these reactions take place at energies well below this barrier due to the effects of quantum tunneling.

### 4.2.1 Compound Nucleus

The exact mechanism of a nuclear reaction is not yet completely understood, but a simple approximation may be used to visualize the process. The first and one of the most useful models was proposed by Bohr in 1936 in which the reaction occurs in two distinct processes. The first is the formation of a 'compound nucleus' which then decomposes into the products. An important corollary of this model is that the compound nucleus 'forgets' how it was formed except that all the fundamental conservation laws remain in effect [2]. As the incident nuclear particle combines with the nucleus, it looses its identity and the total energy of the compound nucleus is shared among all the nuclear particles. In essence the nucleus comes to some form of equilibrium before decomposing with the emission of particles.

The next step in the nuclear reaction is the dissociation of the compound nucleus. This decomposition can take place in numerous ways, usually called the exit channels. These channels are independent of the way in which the nucleus was formed and are only constrained by the conservation of mass-energy, charge, angular momentum, spin, and total momentum. These two steps are considered to be independent of one another. The total amount of excitation energy contained in the nucleus will be given by the equation:

$$U = [M_A / (M_A + M_a)] .T_a + S_a$$

where: U is the excitation energy
$M_A$ is the mass of the target nucleus
$M_a$ is the mass of the incident particle
$T_a$ is the kinetic energy of the incident particle
$S_a$ is the binding energy of the incident particle in the compound nucleus

The nucleus can decompose along several channels as shown in Figure 1.

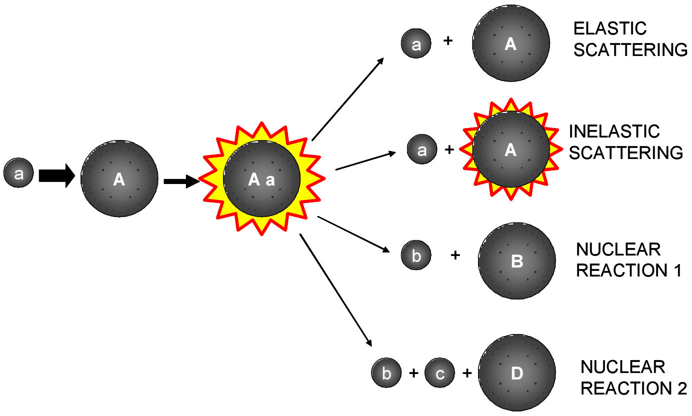


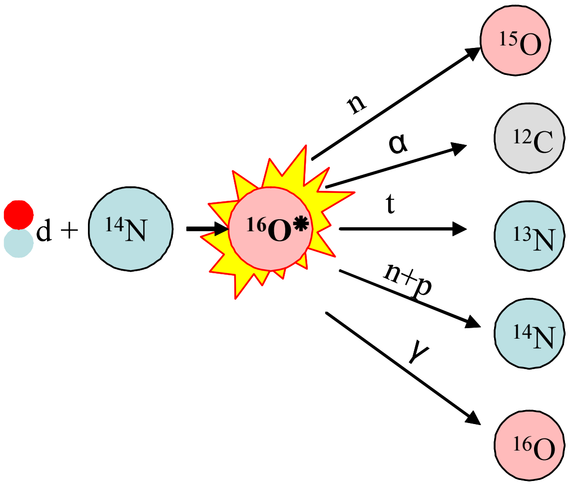
*FIG. 1. Compound Nucleus formation with possible exit channels, the symbol a represents the bombarding particle, and b and c are emitted particles, while A, B and D are the nuclei*

## 4.3 KINEMATICS

When the compound nucleus decomposes, the kinetic energy of all the products may be either greater or less than the total kinetic energy of all the reactants. If the energy of the products is greater, then the reaction is said to be exoergic. If the kinetic energy of the products is less than the reactants, then the reaction is endoergic.

### 4.3.1 Q Values

If the reaction is endoergic, then energy of an amount greater than Q must be supplied in order for the reaction to proceed. The magnitude of this difference is called the Q value. If the reaction is exoergic, Q values are positive. An example of the possible reaction pathways is shown in Figure 2 along with their corresponding Q values. The energy changes in a nuclear reaction are large enough that changes in the mass of the reactants and products are observable.



| Q value | Threshold |
|---|---|
| 5.1 MeV | 0 Mev |
| 13.6 MeV | 0 Mev |
| -4.3 MeV | 4.9 Mev |
| -2.2 MeV | 2.5 Mev |
| 20.7 MeV | 0 Mev |

*FIG. 2. Q values and thresholds of nuclear decomposition for the reaction of a deuteron with a nitrogen-14 nucleus after forming the compound nucleus – $^{16}$O*

The nuclear reaction cross-section represents the total probability that a compound nucleus will be formed and then decomposes along a particular channel. This is often called the excitation function. This function determines the amount of a radionuclide that may be made on a given cyclotron, and the levels of contamination of other radioisotopes which can be present in the target material. A detailed examination of the various theories of how a charged particle interacts with a nucleus to produce a nuclear transformation are beyond the scope of this chapter; but a general description of how this interaction occurs may give an insight into the important parameters in the production of radioisotopes and, therefore, a better 'feel' for what reactions are possible at a given energy. It can also give a perception into how important competing reactions might be under various irradiation conditions.

### 4.3.2 Nomenclature

The nomenclature for nuclear reactions as it is usually used throughout this book needs to be defined. If a carbon-13 nucleus is irradiated with a proton beam to produce a nucleus of nitrogen-13 with a neutron emitted from the compound nucleus, this reaction will be written as $^{13}C(p,n)^{13}N$. In a similar manner, if a neon-20 nucleus is bombarded with a deuteron beam to produce a nucleus of fluorine-18 with the concomitant emission of an alpha particle, this reaction sequence will be abbreviated as $^{20}Ne(d,\alpha)^{18}F$.

### 4.3.3 Model Estimations

Using this model, it is possible to make some observations and predictions on the behavior of the cross-sections of nuclear reactions. The *cross-section* is the probability of a nuclear reaction occurring and is expressed in geometric terms of area (cm$^2$). For any nuclear reaction, the cross-section may be represented by the relation:

$$\sigma_i = \sigma_{com}(P_i/ \Sigma P_i)$$

where, $\sigma_i$ is the cross-section for a particular product i
$\sigma_{com}$ is the cross-section for the formation of the compound nucleus
$P_i$ is the probability of process i
$\Sigma P_i$ is the the sum of the probabilities of all processes

The theoretical representation of $\sigma_{com}$ is complicated, but several qualitative generalizations should be noted (3):

- $\sigma_{com}$ is small but finite for bombarding energies which are far below the coulomb barrier height.
- $\sigma_{com}$ increases very rapidly with incident particle kinetic energy when the kinetic energy is less than the barrier height behaving in a similar manner to a Gamow-type barrier function.
- $\sigma_{com}$ does not reach its maximum at a point where the kinetic energy is equal to the barrier height.
- $\sigma_{com}$ approaches asymptotically a maximum value which is simply the geometrical area of the target nucleus, $\pi R^2$, where R is the nuclear radius, when the kinetic energy is much greater than the barrier height.

From these facts, it is possible to gain some insight into reaction cross-sections. The coulomb barrier for protons on the heavier elements is of the order of 10 MeV. It is, therefore, unlikely that reactions between protons and the heavier nuclei will have a very significant cross-section below this energy. If the particle is an alpha particle, the barrier height increases to 25 MeV, so that this energy is usually required before the cross-section becomes significant. From the Q value of the various reactions, it is possible to estimate where the threshold of a reaction will occur. These rules of thumb can often give insight to the probabilities of the desired and interfering nuclear reactions in a given situation. In a similar vein, it is possible to estimate the energy required to release one neutron, two neutrons. At lower energies on light nuclei, the emission of one neutron usually occurs at energies between 2 to 8 MeV, and the probability decreases or stays the same at energies higher than this.

The second neutron will require energy of between 6 and 12 MeV and so on.There is, of course, some overlap between the emission profiles; but by carefully choosing the energy range of the particles in the target material, it is often possible to minimize one reaction in favor of another.

## 4.4 PRODUCTION RATES AND CROSS SECTIONS

The rate of radionuclide production is dependent on a number of factors including the magnitude of the reaction cross-section as a function of energy, the incident particle energy, the thickness of the target in nuclei per cm$^2$ which will determine the exit particle energy, and the flux (related to beam current) of incoming particles. The rate of production is given by:

$$-\frac{dn}{dt} = R = nI(1-e^{-\lambda t})\int_{E_s}^{E_0} \frac{\sigma(E)}{dE/dx} dE$$

where: R is the number of nuclei formed per second
n is the target thickness in nuclei per cm$^2$
I is the incident particle flux per second and is related to beam current
λ is the decay constant and is equal to ln2/$T_{1/2}$
t is the irradiation time in seconds
σ is the reaction cross-section, or probability of interaction, expressed in cm$^2$ and is a function of energy (see Figure 3)
E is the energy of the incident particles, and
x is the distance traveled by the particle
$\int_{E_s}^{E_0}$ is the integral from the initial to final energy of the incident particle along its path

It is of historical interest to note that the unit for cross-section is the barn which is equivalent to $10^{-24}$ cm$^2$. The expression barn comes from the fact that the probability for a neutron to interact with a target is proportional to the area of the nucleus, which compared to the size of the neutron appeared as big as a barn.

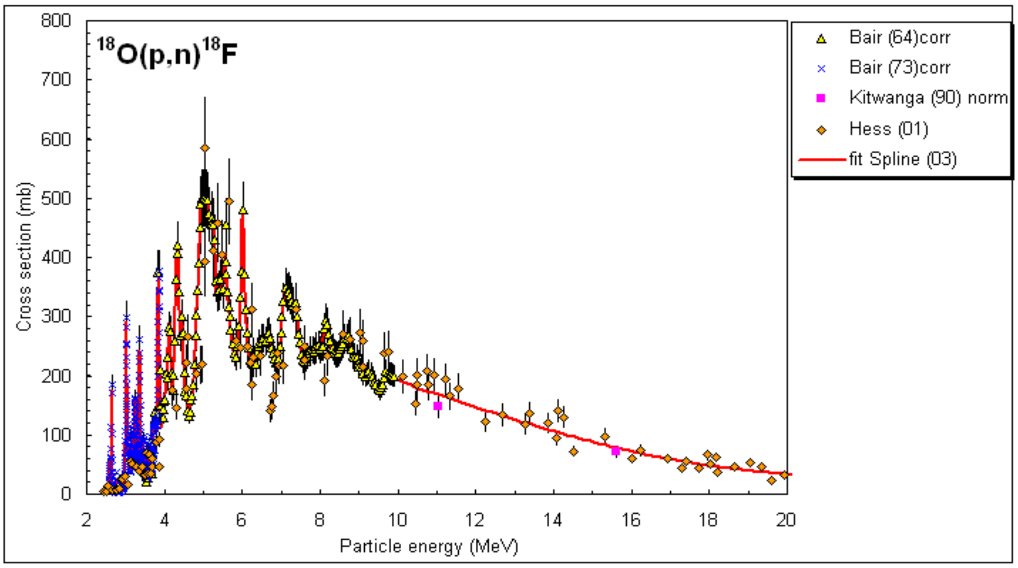


*FIG. 3. Excitation function for the $^{18}$O(p,n)$^{18}$F reaction illustrating energy dependence of cross section σ*

In all cases, the cross-section for a particular reaction should either be taken from the literature or measured since the theoretical estimation of these parameters is not as accurate as could be desired especially on the light nuclei. Experimentally the cross-section of a particular reaction can be reduced to (4):

$$R_i = Inx\sigma_i$$

where, $R_i$ is the number of processes of type i in the target per unit time
I is the number of incident particle per unit time
n is the number of target nuclei per cubic centimeter of target
$\sigma_i$ is the cross-section for the specified process in $cm^2$
x is the the target thickness in centimeters

This relationship is a simplification of the previous equation with a few assumptions. The first is the beam current is constant over the course of the irradiation, the second is the target nuclei are uniformly distributed in the target material, and the third is the cross-section which is independent of energy over the energy range used. The cross-section can then be reduced to:

$$\sigma_i = 2.678 \times 10^{-10} AN_i/It\rho x$$

where, $\sigma_i$ is the cross-section for a process in millibarns for the interval in question
A is the atomic mass of the target material (AMU)
$N_i$ is the number of nuclei created during the irradiation
t is the time of irradiation in seconds
ρ is the density of the target in $g/cm^3$
x is the thickness of the target in cm.
I is the beam current in microamperes

It should be noted that the yields quoted in the literature assume 100% enrichment unless otherwise noted, and the calculation of yields for practical purposes must use the actual enrichment of the target material under consideration. For determining the target thickness, a number of approaches can be used. The easiest method is to use the SRIM (http://www.srim.org/) program which calculates stopping powers for a variety of materials, including compounds. SRIM was developed at the IBM laboratories and is available at no cost on the web.

## 4.5 SATURATION FACTORS AND PRACTICAL YIELDS

The rate of production is, of course, affected by the fact that the resulting nuclide is radioactive and is thus undergoing radioactive decay. For short-lived nuclides, the competition between formation and decay will come to equilibrium at sufficiently long bombardment times. This point is called saturation, meaning that no matter how much longer the irradiation is carried out, the production rate is equal to the rate of decay and the amount of radioactivity stays constant.

### 4.5.1 Radionuclide Production Rates

The rate of formation in this case is given by:

$$R = N \lambda/(1-e^{-\lambda t})$$

where, R is the rate of formation of nuclei
N is the number of target nuclei present at the end
λ the decay constant

The term in the denominator is often referred to as the saturation factor and accounts for the competition of the production of nuclei due to the particle reaction and the radioactive decay of the nuclei which have been produced.

It is clear why the assumption had to be made that the beam current was nearly constant, since a variation in the beam current would affect the relative number of the nuclei being created versus the number being destroyed by decay. If this relation is substituted back into the cross-section equation, then the result is:

$$\sigma_i = 2.678 \times 10^{-10} [A\lambda N_i/(I\rho x(1-e^{-\lambda t}))]$$

where, $\sigma_i$ is the cross-section for process (mb)
A is the atomic mass of the target (AMU)
$\lambda$ is the decay constant for species i ($sec^{-1}$)
$\rho$ is the density of the target material ($g/cm^3$)
t is the time of irradiation (sec)
x is the thickness of the target (cm)
I is the beam current (μA)

It should be noted that the time of irradiation and the decay constant are both given in seconds. This is due to the fact that the beam current is defined in microamperes (μA), which is $6.2 \times 10^{12}$ charges/second.

### 4.5.2 Saturation Factors

At shorter irradiation times, the fraction of product produced is related to the saturation factor given by $(1 - e^{-\lambda t})$, where $\lambda$ is the decay constant of the decaying nuclide and t is the bombardment time. It is evident that an irradiation equivalent to one half-life would result in 50% of saturation. For practical reasons, irradiations rarely exceed three half-lives (90% of saturation) except for the shortest-lived radioisotopes. The practical production limits of a given radionuclide are determined by the half-life of the isotope. It is relatively easy to come near saturation for the production of oxygen-15 with a 2 minute half-life; but it is not reasonable to irradiate a target for the production of fluorine-18 to the point of saturation because of the excessively long times involved. When the saturation factor is plotted as a function of the ratio of the irradiation time to the half-life of the produced radionuclide, it can be clearly seen (in Figure 4) that with increasing half-life, a compromise must be made with respect to expected yield versus the length of the irradiation.

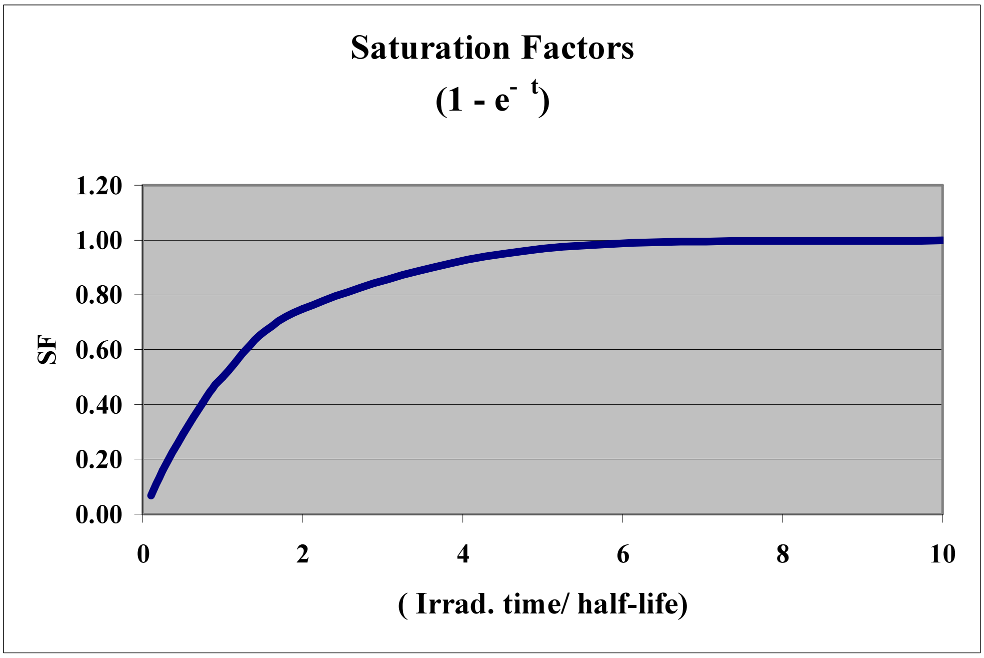


*FIG. 4. Saturation curve as a function of the ratio of irradiation time versus the half-life of the produced radionuclide*

For an irradiation of one half-life, one gets 50% of the saturation yield. For a two half-life irradiation one gets 75%, and so on.

For long-lived species the production rates are usually expressed in terms of integrated dose or total beam flux (μA-hr). For example, with a long-lived radionuclide like $^{82}$Sr (t= 25 d) the amount of radionuclide at the end of bombardment will be essentially the same whether it is produced from 100 μA in 1 hour, or 2 μA in 50 hours (both represent 100 μA-h of beam). For a shorter lived radionuclide like fluorine-18, the two irradiation conditions will produce very different amounts.

In order to optimize the production of a particular radionuclide, the following production considerations must be taken into account:

- the threshold energy for the desired reaction,
- the energy where the maximum yield occurs,
- the chemical form of the target nucleus,
- the physical form of the target nucleus,
- the chemical form of the desired product,
- the physical form of the desired product, and
- the ease of separation of product from the target.

#### *4.5.2.1. Fluorine-18 Example*

To illustrate the application of these estimates, we can look at the case where $^{18}$F is needed as fluoride. The two most widely used nuclear reactions for producing $^{18}$F are the $^{20}$Ne(d,α)$^{18}$F and the $^{18}$O(p,n)$^{18}$F. Both reactions have relatively low threshold energies (0-2 MeV) and the maximum yield occurs at less than 10 MeV for each particle, respectively (see Figures 3 and 5).

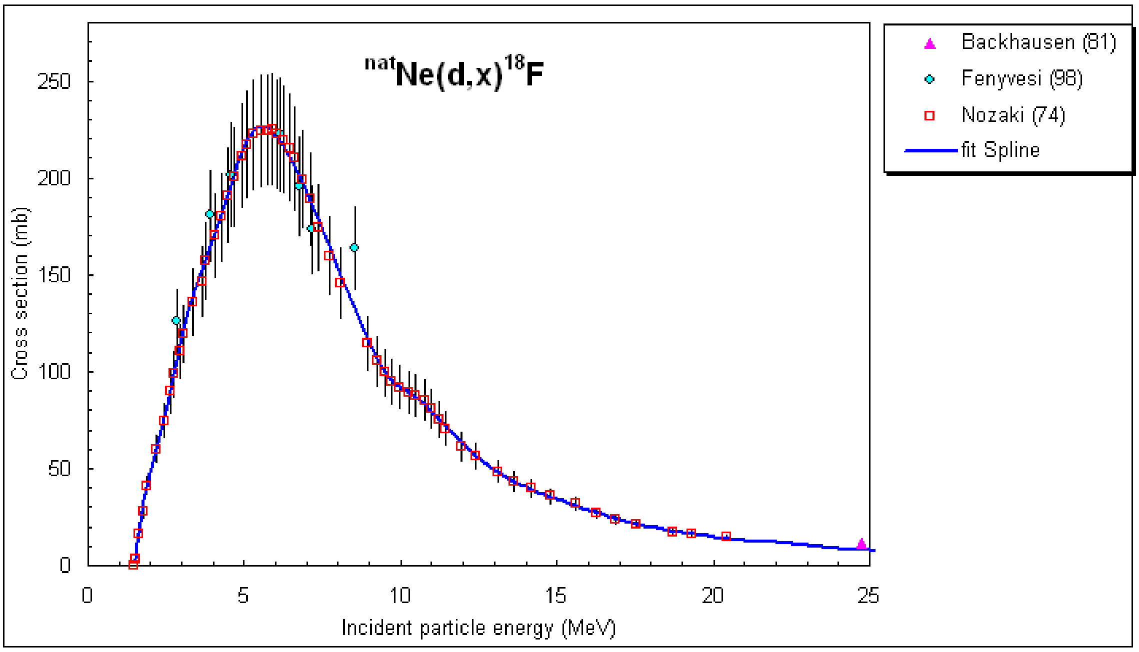


*FIG. 5. Excitation function for the $^{nat}$Ne(d,α)$^{18}$F reaction; the $^{nat}$Ne symbol refers to the fact that the target gas, neon, is of natural isotopic composition ($^{20}$Ne=90.5%, $^{21}$Ne=0.3%, and $^{22}$Ne= 9.2%)*

However, the (p,n) reaction has a much higher cross- section so that the quantity of $^{18}$F that can be produced is more than double for a *thick target* reaction using protons of about 12 MeV in comparison to deuterons of comparable energy. A thick target refers to the situation where the number of target nuclei present is sufficient to lower the beam energy to below the threshold energy for the reaction under consideration. Since both reactions produce the same radionuclide, the saturation factor will be the same assuming we can reach the same beam current with both particles. Having selected the mode of production and the energy, the next issue is to examine the chemical and physical forms of the target and product. The most convenient target material for producing $^{18}$F, as fluoride is a water target enriched in $^{18}$O. The resulting $^{18}$F is produced directly as the fluoride ion which can be extracted from the target water by simple ion exchange columns. Obviously, if the chemical form desired F-18 is elemental fluorine ($F_2$), then a different approach is needed. Elemental F-18 requires the use of non radioactive fluorine carrier through some exchange reaction which is beyond the scope of this section. See the Isotope List for details.

Appendix 2 in the CD attached to this publication gives the detailed calculation of the yield of $^{67}$Ga by $^{68}$Zn(p,2n) $^{67}$Ga reaction in a 30 MeV cyclotron. Appendix 2 also gives details about the hot cell shielding needed for the above production. Appendix 3 is an excel work sheet for the calculation of production yields of $^{67}$Ga, $^{111}$In, $^{201}$Pb($^{201}$Tl) and $^{18}$F by (p, xn) reactions. The dose rates and the lead shielding of hot cells needed are also included.

## 4.6 CONCLUSION

The production of radioisotopes in an accelerator is a complicated process, but understanding a few of the fundamental processes involved in these reactions can make the choice of an appropriate reaction easier. The kinematics of the reaction can determine which radioisotope will predominate in a reaction where several are possible, which in turn affects the usefulness of the radioisotope produced. The irradiation time will depend on the half-life of the desired product and the half-lives of potential contaminants. All these factors must be taken into account when designing a production process [5].

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# 5 TARGETRY

## 5.1 INTRODUCTION

There are literally hundreds of radioisotopes which can be produced with charged particle accelerators. The cyclotron is the most frequent choice, but the linac and other accelerators may become more common with the development of smaller, more reliable machines. This chapter will deal only with the targetry for a small subset of the radionuclides produced with charged particle accelerators.

The goal of cyclotron targetry is to get the target material into the beam, keep it there during the irradiation and to remove the product radionuclide from the target material quickly and efficiently. The specific design of the target is what allows one to achieve this goal. Unless care is taken in the design and fabrication of the target, the production of the radioisotope can be far from optimal and may even be impossible. Over time, many facilities will need to increase the number of radioisotopes being produced or to optimize yields of their currently produced radioisotopes. If they are looking for ways to increase production with commercial targets, modifications of existing targets and procedures, or development of new targets may be a way to accomplish this.

The purpose of this chapter will be to explore some of the problems in the design and construction of cyclotron targets, and to demonstrate with practical examples how to evaluate some solutions to the numerous problems encountered in the optimal design of a cyclotron target. An attempt has been made to present some useful formulas and 'rules of thumb' which may be used in the design of cyclotron targetry. Even if the reader is not designing cyclotron targets, these equations may provide insight into the processes occurring in the targets. The formulas are taken from a number of textbooks on nuclear physics, nuclear chemistry and engineering, and compiled here merely for easy access.

One of the challenges to those involved with the design of targets is that not all cyclotrons are the same. The design of targetry associated with one cyclotron may not be optimal for a different cyclotron. Besides the characteristics of mechanical design, beam energy and beam current, the major variables are the beam size and profile. An uncontrolled or unstable beam profile may result in an unreliable yield of the radioisotope. If the beam profile cannot be controlled, then one must make allowances in the targetry in order to obtain predictable yields. There are often significant differences in the characteristics of the beam profile between a positive ion cyclotron and a negative ion cyclotron. The negative ion cyclotron usually has a more uniform beam profile incident on the target. This is a result of the extraction process through a stripping foil which will scatter, and therefore tend to eliminate hot spots in the beam [1-3]. Focusing magnets and steering magnets along the transport line, if there is one, can alter the beam shape to a more homogeneous one. The positive ion cyclotron may have a uniform beam profile or the profile may be quite 'hot' in spots and not uniform at all, depending on the extraction characteristics and focusing magnets used to transport the beam. In general, the extraction process for positive ions tends to create areas of high intensity in the beam. Most of the newer, commercially available cyclotrons for Positron Emission Tomography (PET), are negative ion cyclotrons and have targets mounted directly on the cyclotron without any focusing or steering magnets to alter the beam shape.

Other factors which are important for effective radioisotope production are whether or not an internal beam is available, and whether or not multiple targets can be irradiated simultaneously. Internal targets were first developed because the extraction efficiency of older cyclotrons was quite low.

The extraction efficiency of a cyclotron is defined as the beam current extracted from the machine divided by the beam current circulating before extraction. In the older positive ion cyclotrons, a great deal of the beam was lost inside the machine (an extraction efficiency of 10% being thought quite acceptable, although more modern positive ion machines are capable of extracting more than 60% of the beam). The use of negative ion cyclotrons and the greatly improved extraction efficiency of newer positive ion cyclotrons have reduced the need for internal targets, but they are still quite common since they work well. The internal target is usually set as a grazing incidence target, because this allows the heat generated from the target to be dispersed over a wider area. The negative ion cyclotron allows for the irradiation of multiple targets simultaneously. This is not usually possible with the positive ion cyclotron, unless the targets are 'piggyback' or 'tandem' targets with one target following another along the same beam line.

A great deal of useful information about targets and target chemistry can be found in a book by Clark and Buckingham [4] and in the proceedings of the International Workshop on Targets and Target Chemistry. These proceedings are available on line through the courtesy of TRIUMF at http://www.triumf.ca/wttc/proceedings.html. These are very valuable resources for all who are concerned with the production of radioisotopes.

## 5.2 TARGET TYPES

For production of radioisotopes, the target material may be either gas, liquid or solid. Targets are, consequently, designed to accommodate the material being irradiated. The design of the target will also depend on whether the target is placed inside (internal) or outside (external) to the cyclotron.

### 5.2.1 Internal Targets

Internal targets were the first targets used in cyclotrons. The real advantage of these targets today is that the target may be built to exactly match the beam curvature and, therefore, spread the power of the beam over the maximum area and increase the amount of beam current which may be applied to the target. A schematic of an internal target is shown in Figure 1.

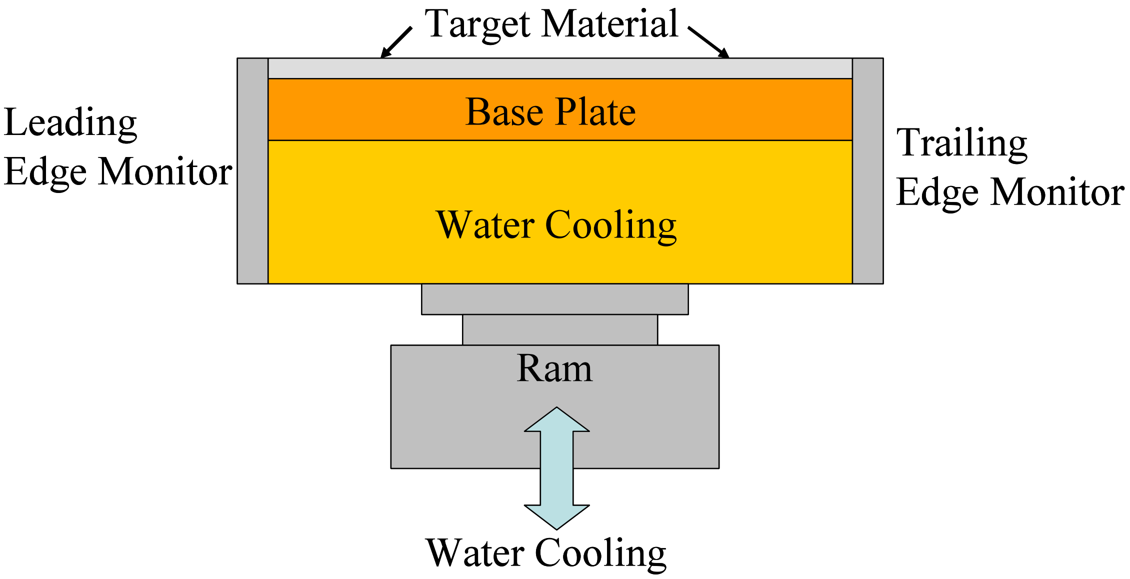

*FIG. 1. Schematic diagram of an internal target showing a plated surface in a base plate for cooling*

These targets are very widely used today for the production of non-volatile solid radioisotopes such as $^{123}$I, $^{124}$I, $^{201}$Tl, $^{67}$Ga, and $^{111}$In. The target material is typically a solid, usually in the form of a thin metal layer, although internal targets using powders and liquids have been designed and used.

Figure 2 shows a typical internal target used for the production of radioisotopes for nuclear medicine. This particular target was used for the production of $^{201}$Tl. The thallium is electroplated onto the copper surface and then dissolved after irradiation [5].

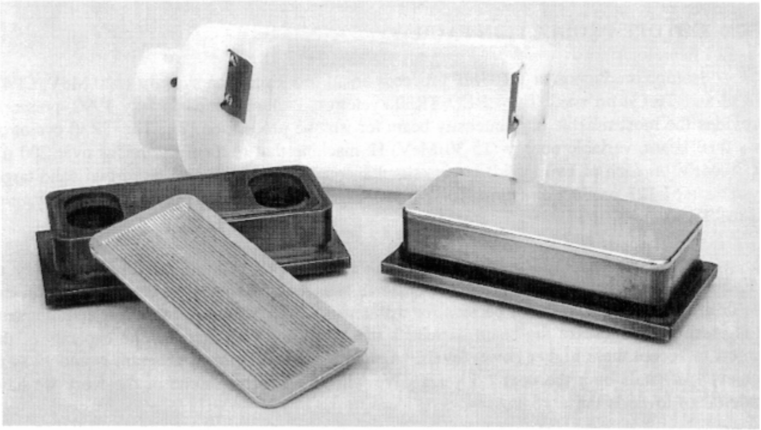

*FIG. 2. Internal target used for production of Tl-201*

An example of an internal powder target is shown in Figure 3 [6]. This particular target was used to produce $^{123}$I from $^{122}$Te, using deuterons as the bombarding particle. The $^{123}$I is swept out of the target by the helium gas flow and the target never has to be removed from the cyclotron except for maintenance.

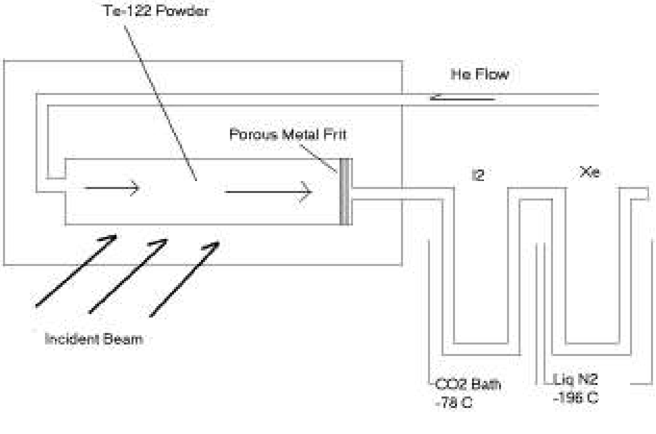

*FIG. 3. An example of an internal target using $^{122}$Te powder to produce $^{123}$I*

### 5.2.2 External Targets

There are a very wide variety of external targets which can be used for irradiation of solids, liquids, and gases. It is impossible to give a complete description of all the designs. What follows is a general description of each of these target types.

### *5.2.2.1. Solid Targets*

Because the density of solids is typically higher than that of liquids or gases, the path length of the beam is shorter, and the target somewhat smaller. The solid can be in the form of a foil or a powder. If the solid is a good heat conductor, then the beam can be perpendicular to the solid. A typical solid target for conductive powders is shown in Figure 4.

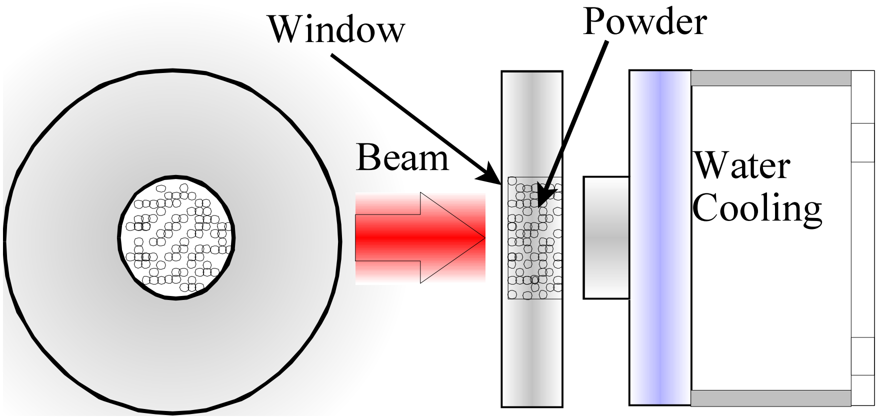

*FIG. 4. Typical solid powder target for use with low beam current or with thermally conductive solids*

A picture of a typical external solid target is shown in Figure 5. The powder is held in the small cavity. The cover foil is shown next to the cavity.

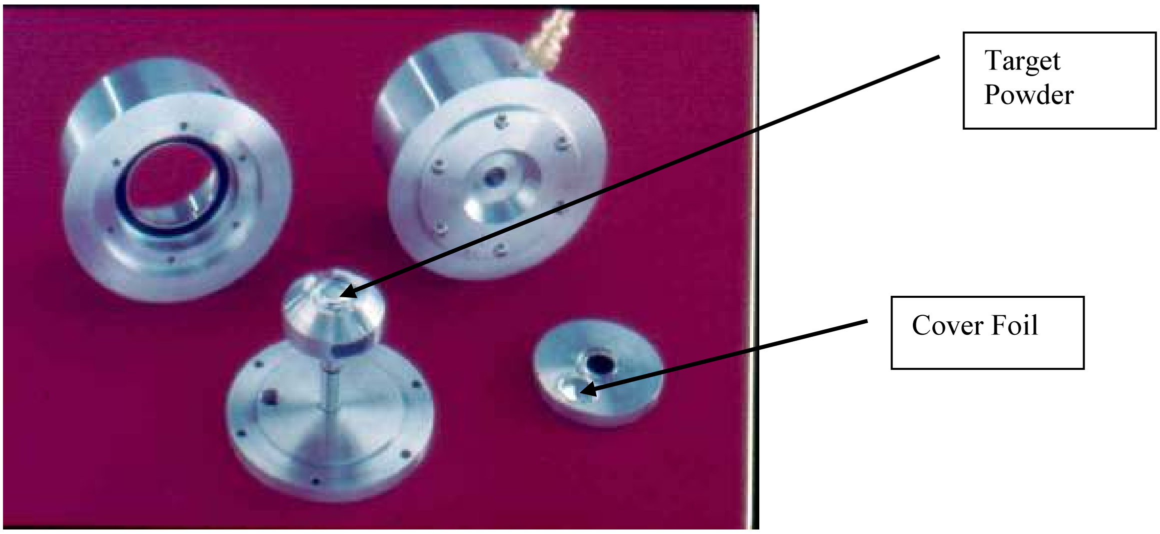

*FIG. 5. Picture of solid powder target used at Brookhaven National Laboratory*

If the solid is not a good thermal conductor or when very high beam currents are used, it is typical to form the solid on an inclined plane (see section 5.5.4).

### *5.2.2.2. Liquid Targets*

In the case of liquids, the target has similar dimensions to the solid target since the target material occupies a specific volume unless the liquid volatilizes. The difference is that the liquid is typically added and removed from the target while it is in place on the cyclotron. A typical liquid target for the production of fluorine-18 from oxygen-18 water is shown in Figures 6 and 7.

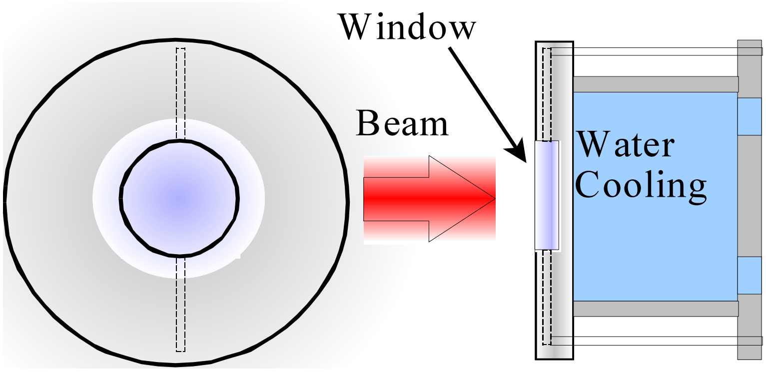

*FIG. 6. Schematic diagram of a typical external target used for irradiating liquids. This particular target is constructed of silver and is used to produce* $^{18}$*F from* $^{18}$*O enriched water.*

*FIG. 7. Picture of* $^{18}$*O water target from the Pulsar linear accelerator from AccSys. Note the grid covering the front foil to enable front foil to withstand higher pressures and beam currents.*

### *5.2.2.3. Gas Targets*

Gas targets are widely used and are usually some type of cylinder to hold the gas under pressure with a thin beam entry foil usually referred to as a window. The principal constraint on the gas target is to remove the heat from the gas since gases are not very good heat conductors and the targets must be quite large in comparison to solid or liquid targets in order to hold the necessary amount of material. A schematic diagram of a typical gas target is shown in Figure 8.

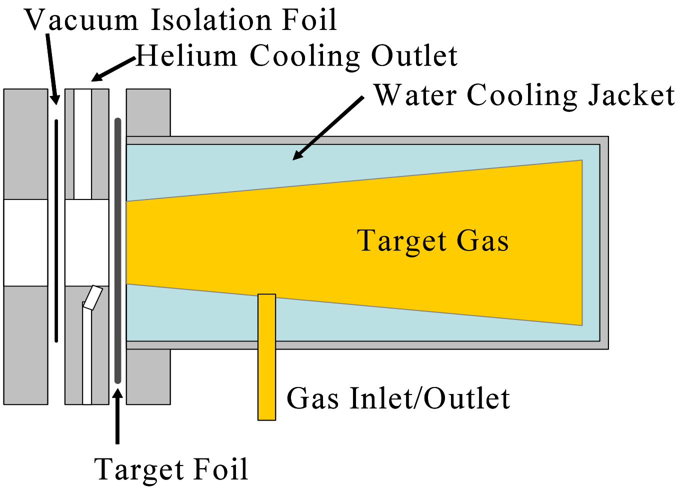

*FIG. 8. Schematic diagram of a typical gas target showing the chamber for the gas cut at an angle to account for the multiple scattering.*

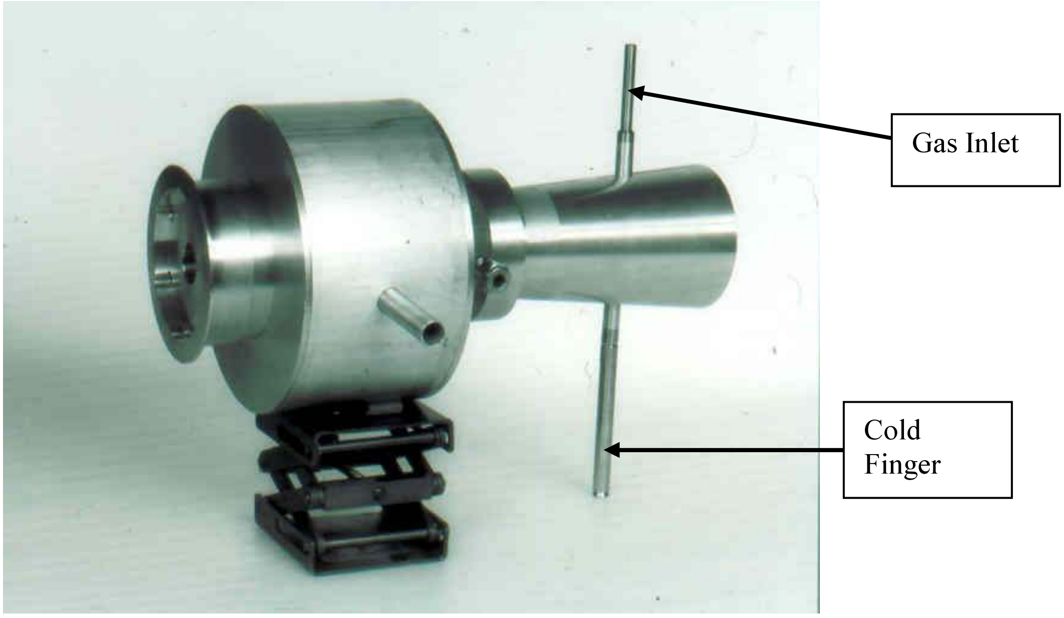

*FIG. 9. Picture of a gas target used for the production of $^{123}$I from $^{124}$Xe.*

The coldfinger on the bottom of the target allows the gas to be transferred into the target more efficiently. The large volume in the front of the target was used to capture the xenon if the front foil ruptured

The design and construction of cyclotron targets is a multidisplinary field. Engineering, Physics and Chemistry each plays an important part in the way cyclotron targets are constructed. In almost all cases, it is necessary to make some compromises in the design, since very often the best solution of a problem with one aspect of the target will introduce an unacceptable constraint on another aspect of the target.

## 5.3 APPLICATION OF PHYSICS TO TARGETRY

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. Factors to be considered in relation to thermodynamics include: interactions of charged particles with matter; stopping power and ranges; energy straggling; and small angle multiple scattering. Each of these factors will be described in some detail.

### 5.3.1 Interactions of Charged Particles with Matter

As a charged particle moves through the surrounding medium, it interacts through ionization, scattering, and various types of radiative losses. There are four main processes involved.

In the first process, the particles will undergo inelastic collisions with the atomic electrons of the surrounding medium. In this case the electrons are promoted to a higher energy level (excitation), or an unbound state (ionization) [1]. If ionization occurs, then the ions and electrons recombine to form an excited neutral atom or molecule. In either case, the excited atom or molecule must transfer the excess energy to the surrounding molecules. The transfer of energy from the charged particle to the surrounding medium in this fashion is the primary energy loss mechanism for the charged particle beam and the major source of heat in the target material.

The second mode of interaction is the inelastic collision with a nucleus of the target material. In this case the charged particle is deflected by some amount, depending on the proximity of the encounter and the charges involved. In some of these deflections, a quantum of energy is lost from radiation (bremsstrahlung) and a corresponding amount of kinetic energy is lost from the colliding pair. The total bremsstrahlung intensity varies inversely with the square of the mass of the charged particle, so that it is not usually important for protons or more massive particles.

The third means of interaction is the elastic collision with a nucleus. In the elastic collision, the incident particle is deflected, but does not radiate nor result in any excitation of the target nucleus. The only kinetic energy lost is due to conservation of momentum by the deflection of the particle. This process is common for electrons, but is much less probable for charged particles.

The last mode of interaction is the elastic collision with atomic electrons. This process usually occurs only at low energy when the charged particle does not transfer enough energy to the atomic electron to promote it to the lowest excited state energy level.

The charged particle loses energy as a result of all four of these processes as it moves through the target material. 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 behavior of the beam can be predicted with high accuracy and reliability.

### 5.3.2 Stopping Power and Ranges

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

Stopping power S(E) = - dE/dx

where E is the particle energy (MeV)
x is the distance traveled (cm)

The exact calculation of this quantity is complex but a reasonable approximation may be obtained rather easily (1). The result is

$$\frac{-dE}{dx} = \frac{(4\pi z^2 e^4 NZ)}{m_0 V^2 A} \ln(\frac{2m_0 V^2}{I})$$

where: z is the particle atomic number (amu)
Z is the absorber atomic number (amu)
e is the electronic charge (esu)
$m_o$ is the rest mass of the electron (MeV)
A is the atomic mass number of the absorber (amu)
V is the particle velocity (cm/sec)
N is the Avogadro's number
I is the ionization potential of the absorber (eV)

The assumption is made in the above approximation that the particle is massive in comparison to the electron. This assumption leads to a maximum energy transfer of $2m_oV^2$. Therefore, the above expression can be reduced to the following formula:

$$\frac{-dE}{dx} = \frac{144Zz^2}{AE}\ln(\frac{2195E}{I})$$

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)
I is the absorber effective ionization potential (eV)

If the effective ionization potential is known, then it may be used. Tables of the effective ionization potential of atoms may be found in Janni [7] or on the SRIM web site (http://www.srim.org/). If it is not known, it may be approximated by the following relations [7]:

$I = 13Z$ for $Z \leq 13$
$I = 9.76Z + 58.8Z^{-.019}$ for $Z > 13$

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

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

where S(E) is the stopping power at energy E

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

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

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

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. Using this formula and an integration interval of 0.1 MeV, a range of 20 MeV protons on aluminum was determined to be 0.5808 g/cm$^2$. The value from the tables of Williamson, Boujot and Picard is 0.5740 g/cm$^2$. Thus, it can be seen that the values agree within about 1-2%. The agreement is better at lower energies and somewhat worse at higher energies, although the agreement is nearly always better than about 2% at energies typical of a radioisotope production cyclotron [8]. The following table 1 is for protons on aluminum.

TABLE 1. RANGES (g/cm$^2$) OF PROTONS ON ALUMINUM CALCULATED BY DIFFERENT METHODS.

| Energy (MeV) | Range (Simple) | Range SRIM | Range Janni | Range WG&J |
|---|---|---|---|---|
| 15 | 0.3477 | 0.3431 | 0.3430 | 0.3448 |
| 14 | 0.3077 | 0.3026 | 0.3038 | 0.3053 |
| 13 | 0.2699 | 0.2662 | 0.2668 | 0.2679 |
| 12 | 0.2344 | 0.2313 | 0.2319 | 0.2327 |
| 11 | 0.2011 | 0.1987 | 0.1992 | 0.1998 |
| 10 | 0.1702 | 0.1681 | 0.1687 | 0.1691 |

| | | | | |
|---|---|---|---|---|
| 9 | 0.1416 | 0.1401 | 0.1405 | 0.1407 |
| 8 | 0.1155 | 0.1142 | 0.1146 | 0.1147 |
| 7 | 0.0917 | 0.0907 | 0.0910 | 0.0910 |
| 6 | 0.0705 | 0.0696 | 0.0699 | 0.0698 |
| 5 | 0.0517 | 0.0511 | 0.0513 | 0.0511 |
| 4 | 0.0357 | 0.0350 | 0.0352 | 0.0351 |
| 3 | 0.0223 | 0.0217 | 0.0219 | 0.0218 |
| 2 | 0.0118 | 0.0112 | 0.0114 | 0.0113 |
| 1 | 0.0044 | 0.0039 | 0.0040 | 0.0039 |

There are two other considerations in the calculation of the range of a particle for cyclotron targetry. These are the ranges of particles other than protons, and the other is the range in a compound made up of several elements so that the ionization potential, atomic number, and atomic mass are a composite of the elements.

In the case of the stopping power, the relation that is usually used to calculate the range of particles other than the proton is that the stopping power for these particles can be related to the stopping power of the proton in the following fashion [7]:

| | |
|---|---|
| deuterons | $S_d(E) = S_p(E/2)$ |
| tritons | $S_t(E) = S_p(E/3)$ |
| helium-3 | $S_{He\text{-}3}(E) = 4S_p(E/3)$ |
| helium-4 | $S_{He\text{-}4}(E) = 4S_p(E/4)$ |

These relationships are valid above the energy where the ion charge has reached its maximum (for $^4$He this is about 1.7 MeV). In a similar fashion, the stopping power of a particle in a chemical compound, alloy or composite material is the stopping power of the particle in each element of the compound times the atom fraction of that element in the compound. The stopping power and ranges may also be obtained from a computer code called SRIM, which is available at no cost on the web (http://www.srim.org/).

### 5.3.3 Energy Straggling

Charged particles having the same initialvelocity do not travel the same distance through the absorbing medium. The ranges of an initially monoenergetic source will have a distribution of ranges centered about the mean range of the particles due to the statistical nature of the atomic collision processes described earlier. This phenomenon is referred to as energy straggling and has a significant application to cyclotron targetry in determining the expected yield from a target which does not stop all the incident charged particles. In this situation, a foil used to degrade the energy of the beam can have a significant effect on the yield from a target, even if the calculated energy of the beam is the same as that of a beam which enters the target without passing through a degrader foil. As an example, the figure 10 shows the distribution of energies resulting from degrading the beam energy from 200 MeV to 15 MeV, from 70 MeV to 15 MeV, and from 30 MeV to 15 MeV, all with the same number of particles.

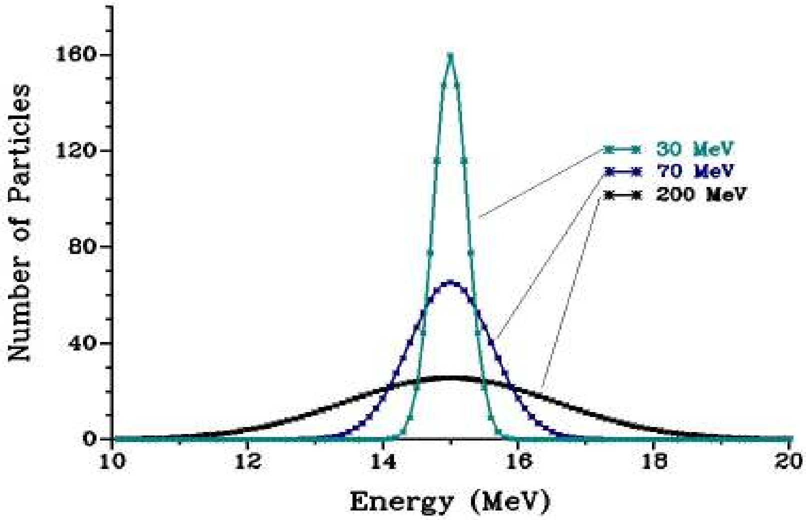

*FIG. 10. Distribution of beam energy when protons are degraded from an initial energy of 200, 70 or 30 MeV to a final energy of 15 MeV*

It is clear that if the initial energy of 30 MeV will have an energy spread of about 2 MeV, whereas if the initial energy is 200 MeV, the energy spread is near 10 MeV. A beam with an initial energy $E_o$ traveling through an absorber will lose energy according to the stopping power equation. The average distance the particles will have traveled when they reach the energy $E_1$ is given by the relation (2).

$$\bar{x} = \int_{E_1}^{E_0} \frac{1}{S(E)} dE$$

The distribution of distances traveled by the individual particles is approximately Gaussian. Another way to look at this is to say that at a given point in the absorber, the particles will have a distribution of energies. The standard deviation of this straggling function can be approximated quite accurately by the relation:

$$\sigma = 0.395 z \left( \frac{Z}{A} x \right)^{1/2} \quad \text{(MeV)}$$

where z is the projectile atomic number (amu)
Z is the absorber atomic number (amu)
A is the absorber atomic mass number (amu)
x is the particle path length (g/cm$^2$)

The straggling function is assumed to be Gaussian and the sigma is in units of MeV. This expression is not valid at very short ranges (less than 1% energy loss), or at very long ranges, where the particle energy is near thermal energies (beam stopped completely).

### 5.3.4 Small Angle Multiple Scattering

As the particles travel through the absorber, they also undergo small angle multiple scattering. Small angle multiple scattering has an important implication on the design of cyclotron targets, because any foils or target material in the beam path will spread the beam. The shape of the target must account for this increase in beam diameter if we want to maximize the yield. This is especially important in the design of gas targets, since the target medium is usually at a lower density than a liquid or solid target and, therefore, must be longer and the effects of the small angle multiple scattering will be greater. In the normal analysis of the scattering angle, the large angle scattering is ignored since the fraction of particles which are scattered by this mechanism is rather small and, therefore, not of great importance to the yield from the target. The sigma of the scattering angle may be approximated by the relation [3]:

$$\sigma^2 = QG$$

where $\sigma$ is the standard deviation of a Gaussian distribution

The term Q is given by:

$$Q = \frac{4\pi\phi I e^4 Z^2 z^2}{p^2 v^2}$$

where z is the atomic number of the particle (amu)
Z is the atomic number of the absorber (amu)
e is the electronic charge (esu)
p is the particle momentum (g-cm/sec)
v is the particle velocity (cm/sec)
$\Phi$ is the number density (atoms/cc)
I is the thickness of the absorber (cm)

and the term G is given by:

$$G = 0.5\ln\left(\frac{Ea_0}{zZ^{4/3}e^2}\right)$$

These two relations can be combined and simplified to the relation:

$$\sigma^2 = 0.0536\left[\frac{xZ^2z^2\ln\left(\frac{3.67\times10^4 E}{zZ^{4/3}}\right)}{AE^2}\right]$$

where x is the density of the absorber (g/cm$^2$)
E is the projectile energy (MeV)
A is the absorber atomic mass (amu)
z is the atomic number of the particle (amu)
Z is the atomic number of the absorber (amu)

This approximation is correct to within a few percent if the energy used is the average energy of the beam in the absorber. The angular distribution can also be obtained by using the program SRIM which is available on the internet (http://www.srim.org/).

The initial distribution of the beam may be approximated with any degree of resolution from the simple step function to a more accurate and complex function determined with a beam profile monitor. In practice, one may approximate the shape of the beam by dividing the beam into smaller segments (as many as one feels are necessary for accuracy) and then multiplying each segment by a Gaussian function with a standard deviation (sigma) derived from the equation. Each of these segments are overlaid with each other in space, and summed. The function after scattering is then normalized to the known beam current. This gives a good approximation to the beam profile. The relation is less accurate where the path length is very long and the energy at the exit from the absorber is near zero. In this situation, a more accurate approximation may be achieved by separating the total range of the particle into smaller segments. One then calculates the beam distribution in the first segment, and uses the output of that segment as the input to the next segment.

## 5.4 APPLICATION OF CHEMISTRY TO TARGETRY

The chemistry occurring inside a cyclotron target is the source for the chemical products which are produced during irradiation. The reactions of the highly excited nucleogenic atom with its surroundings during the de-excitation are the determining factor in which radiolabeled molecules will be formed. Many of the chemical reactions occurring were first studied using hot atom chemistry. A 'hot atom' is an atom formed nucleogenically with a great deal of excess energy. However, the conditions inside the production target are quite different from a typical hot atom experiment. In the case of a hot atom experiment, the beam current is usually less than one microampere and the gas is at a pressure of much less than one atmosphere. In a normal production gas target, the beam current may be 20 or 30 microamperes (or higher with the newer targets) and pressure up to 70 atmospheres. However, in many cases the results from hot atom experiments have been very successful in explaining the product distributions from production gas targets.

### 5.4.1 Chemical Interactions in the Target

The state of the matter inside a cyclotron target depends on the state of the matter being bombarded. In a gas target, the gas is highly ionized and ion-molecule and highly endothermic reactions are occurring. A view inside the target during irradiation is shown in Figure 11.

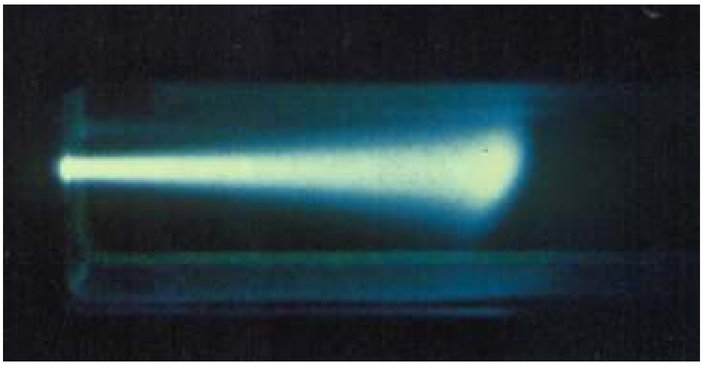

*FIG. 11. View inside a gas target during irradiation where the highly excited and ionized gas molecules emit light and heat (Picture courtesy of Sven-Johan Heselius)*

Nearly any chemical species can be formed in this gaseous plasma or 'ionic soup'. When other gases are present, either as contaminants or as additives, the situation becomes very complex. In most cases, the final product distribution will be determined by the thermodynamics of the situation since there is more than enough energy to overcome the kinetic activation barriers which would place constraints on the product distribution at lower temperatures. In a liquid target, the material may be as a liquid or as a vapor, depending on the beam density and temperature. The target material may boil intermittently as has been seen in water targets for the production of fluorine-18 [9, 10]. An example of the water boiling and the excited water molecules giving off light is shown in Figure 12.

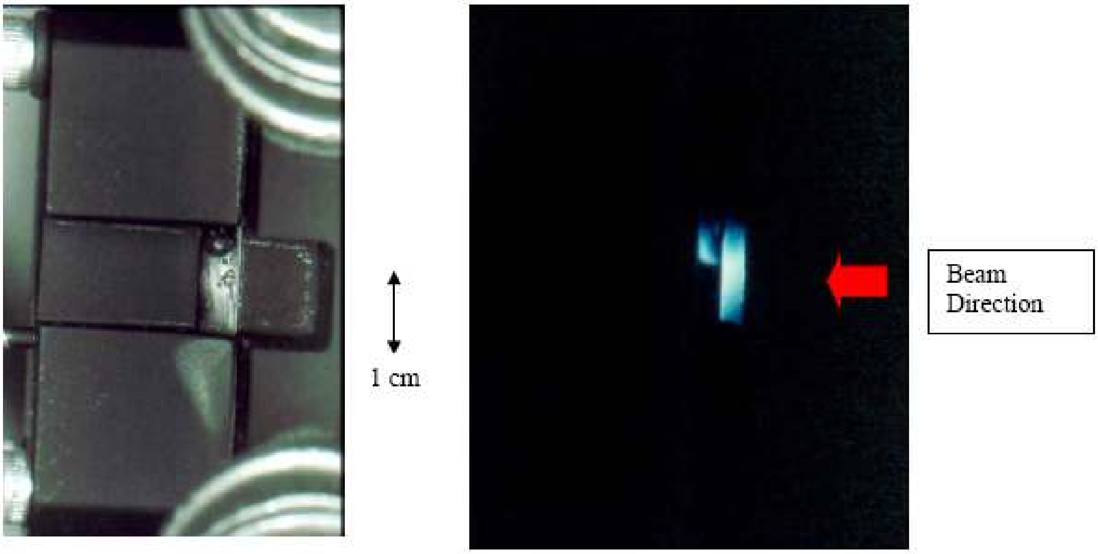

*FIG. 12. Water boiling and emitting light during irradiation*

In a solid target, the solid may liquefy or sublime and change the physical state of the target. The final chemical form of the radionuclide from a gas target depends on the gases which are present in the mixture. As an example, the production of $^{11}CO_2$ from the $^{14}N(p,\alpha)^{11}C$ reaction in pure nitrogen gas. Nitrogen gas obtained from any commercial source contains at least 0.5 ppm of oxygen as an impurity.

This quantity is usually sufficient to convert all hydrocarbon impurities to $CO_2$ with enough $O_2$ left over to convert all the carbon-11 produced in the target to carbon dioxide, if the carbon does not get to the walls of the target before it is thermalized. If other chemical forms of carbon are desired, then another gas must be added in great excess, since the reaction with oxygen is such a thermodynamically favorable one. If the desired product is methane, then about 5% $H_2$ must be added to the gas in order to ensure that methane will be the final product [11, 12]. It is thought that the reason carbon dioxide is not the final product is because the hydrogen reacts with the oxygen to produce water and, therefore, is not available to form carbon dioxide. There is almost certainly hydrogen cyanide produced in this same target, but the thermal energy is high enough that this product is quickly converted to the more thermodynamically stable methane and ammonia. Another processing step must be done outside the target to convert the methane and ammonia back to hydrogen cyanide, which is often the desired product. The thermodynamic stability of the molecules is often the determining factor in the final product distribution. The large amounts of energy present in the target during irradiation make the kinetics of the reactions less important than the thermodynamics since most activation barriers are easily overcome.

One development in targetry has been the use of mixed phase targets to alter the chemical form of the radionuclide. One example of this is the carbon-13 powder water slurry target developed by CTI [13]. In this target, the slurry of carbon-13 powder in water is irradiated in the cyclotron beam to produce $^{13}NH_3$. A schematic diagram of the target is shown in Figure 13.

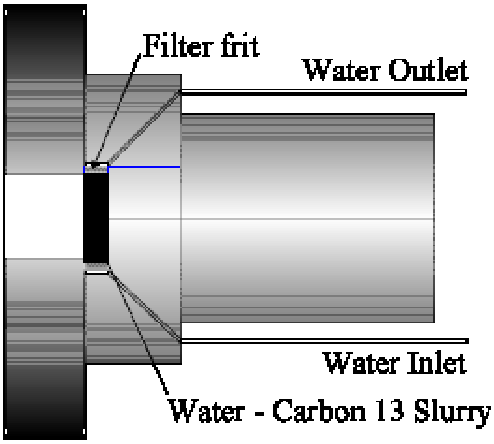

*FIG. 13. Carbon-13 slurry target developed by CTI, Inc for the production of N-13 ammonia*

This is interesting since the water target has been used for many years to produce nitrogen-13 but the chemical form was as nitrates and nitrites, which were then converted to ammonia by reduction with Devarda's alloy in base or with $TiCl_3$. The carbon-13 carbon powder produces nitrogen-13 from the $^{13}C(p,n)^{13}N$ nuclear reaction as well as the $^{16}O(p,\alpha)^{13}N$ nuclear reaction on the oxygen in the water. There is some question whether much $^{13}N$ is coming from $^{13}C$ or is locked tightly in the matrix. The fact that the product is nitrogen-13 ammonia suggests that the carbon powder is removing or at least binding the oxygen dissolved in the water so that it cannot react with the atomic nitrogen produced. Another example of additives used to make ammonia directly in the target is with the addition of ethanol to the water target. A few parts per thousand of ethanol will change the chemical form of the nitrogen-13 from nitrate and nitrites to ammonia. The exact nature of the effects of these additives is still under study. This type of ‘in-target’ chemistry offers opportunities for altering the chemical form of the radioisotope in many ways, depending on the properties of the target material and the additives [14].

### 5.4.2 Specific Activity and Contaminants in the Target Material

The specific activity of a radionuclide is defined as the quantity of radionuclide divided by the total mass of the compound. As an example, if a sample of carbon-11 carbon dioxide is measured to have 200 mCi and the amount of mass is determined to be 0.1 μmoles, then the specific activity is 2 Ci/μmole. There is, of course, an ultimate limit, which occurs when only the radioactive atoms or radiolabeled molecules are present. A list of some common PET radionuclides and some relevant information is given in Table 2 [15].

TABLE 2. COMMON PET RADIONUCLIDES AND THEIR DECAY CHARACTERISTICS

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

| | | | | | | |
|---|---|---|---|---|---|---|
| I-124 | 6019.2 | 23.3%$\beta^+$ | 2.13 MeV | 0.8 MeV | 10.2 mm | 31 |

The specific activity is a critical factor for some types of clinical agents and radiotracers for biological work. The radiotracers used to probe brain chemistry and receptor occupancy are examples of this need for high specific activity, or more correctly low injected mass. Mass in excess of a few nanomoles can have an effect on the receptor occupancy and, therefore, alter the apparent receptor characteristics with respect to those observed with high specific activity (low mass) radiotracers. The specific activity of the radiotracer should be monitored and if the amount of mass is too great or starts to increase, then steps should be taken to remedy the situation. The sources of carrier in the final product may be the chemicals used in the synthesis of the radiotracer, or in the target material, or target walls, foils, etc.

The only way to determine the source of the carrier is to measure the specific activity at each step in the processing of the target material to the final radiotracer preparation. The methods for measuring the specific activity of the target material after irradiation will depend on the physical state of the target material. Gaseous target material can often be analyzed with the use of radio gas chromatography, using flame ionization detectors, nitrogen phosphorus detectors, or electron capture detectors. Liquids can often be analyzed with high pressure liquid chromatography or ion chromatography, using ultraviolet and conductivity detectors, respectively. The solid target material poses the most difficult problems. These materials can sometimes be analyzed by X ray fluorescence or mass spectrometry.

A major concern in PET is the specific activity of the carbon-11. Carbon can come from the walls of the target during irradiation. This amount of carbon can be reduced by irradiating an inert gas mixture with oxygen in the target. If the target is kept leak tight and pressurized, the amount of carrier carbon should remain low. The quantity of activity recovered from the target is often reduced as the specific activity is increased. The yields can be increased by adding additional oxygen to the nitrogen gas. Further examples of target care are provided in Chapter 6.

The carrier fluoride in the water target used for the production of [$^{18}$F] fluoride is another case in point. Here the specific activity is often limited by the amount of carrier fluoride in the oxygen-18 enriched water used.

It has been shown that the amount of fluoride does not increase on prolonged irradiation as was the case with carbon-11. This suggests that the target 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, which are manufactured with fluorine in some form or another. This makes it very difficult to obtain very high specific activity [$^{18}$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 3.

TABLE 3. FLUORINE IN COMMON MATERIALS

| **Material** | **Fluorine (wt %)** |
|---|---|
| Teflon (PTFE) | 76 |
| Kel-F | 49 |
| Needle valve packing material | 50 |
| Viton | 0.002 |
| Polyethylene | N.D. (< 0.0004%) |

### 5.4.3 Target Temperatures

The temperature inside the target will have an effect on the product distribution. The effect of temperature on the density reduction has already been mentioned [10]. Temperatures inside an argon gas target are given in Figures 14 and 15. In both cases the beam was protons at 14.7 MeV and a current of 15 µA incident on the gas and the beam has a range longer than the target.

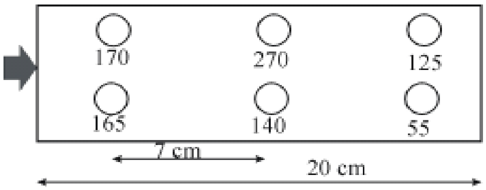

*FIG. 14. Temperatures in six regions of the target at a gas pressure of 675 kPa*

The temperatures are shown at two different pressures of gas in the target. Figure 14 shows the temperatures recorded at a pressure of 675 kPa and Figure 15 shows the temperatures at a pressure of 550 kPa.

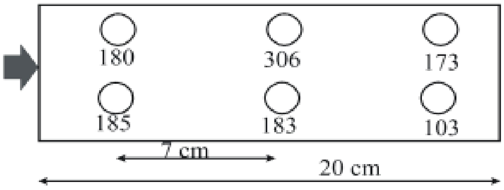

*FIG. 15. Temperatures in six regions of the target at a gas pressure of 550 kPa.*

As can be seen from these typical temperatures, the temperatures can be quite high and most kinetic barriers can be easily overcome. The thermodynamics of the particular components of the system are, therefore, likely to determine the final chemical form of the radioisotope.

The temperatures inside a water target during bombardment have been published [9, 16]. Under the conditions of normal production, the temperature of the water attained the boiling point and stayed at this point during the irradiation. When pressure was put on the target, the temperature of the target water went up to the boiling point of water at that pressure. When the target is boiling, the production of the radioisotope is lower than if the target remained as a liquid. This is based on the assumption that the range of the particles in the target is similar to the dimensions. One can make the target much longer than the dimensions of the particle path to increase yield while boiling. This technique has been used on several commercial targets. These observations show that density reduction is at work in nearly all gaseous and liquid targets to one extent or another, and yields can be increased by compensating for this phenomenon.

### 5.4.4 Radiation Damage

Another problem in cyclotron targetry is the degradation of certain materials with radiation exposure. Gamma and beta radiation have little effect on metals, but they break the chemical bonds and prevent bond recombination of organic compounds. This is particularly true of plastics, where some are quite radiation resistant while others degrade under prolonged exposure. For a given gamma or neutron flux, the degree of degradation observed depends on the type of chemical bonding present. The chemical bond with the least resistance to decomposition is the covalent bond. There is considerable variation in the strength of covalent bonds present in different plastics and a wide variation in their stability under radiation. Common chemical reactions that take place in organic compounds during irradiation are polymerization, oxidation, halogenation, and changes in isomerism. A short list of some common plastic materials used in cyclotron targets and their radiation resistance is given in Table 4.

TABLE 4. SUSCEPTIBILITY OF MATERIALS TO RADIATION DAMAGE

| Material | Radiation Resistance | Tolerance Level (kGy) |
|---|---|---|
| Teflon | poor (becomes powdery) | 5 |
| Polyethelyene | good | 1,000 |
| Polypropylene | fair | 50 |
| PEEK (Polyethyletherketone) | excellent | 10,000 |
| Nylon (aliphatic or amorphous) | fair | 50 |
| Polycarbonate | good | 1,000 |
| Polystyrene | excellent | 10,000 |

## 5.5 APPLICATION OF ENGINEERING TO TARGETRY

### 5.5.1 Heat Transfer

As was mentioned earlier, the energy lost when charged particles pass through the target medium is dissipated in the form of heat. One of the most challenging problems in the design of cyclotron targets is finding methods to remove this heat from the target during irradiation. The heat generated in the target can often have several detrimental effects. A few of these have been discussed already such as target density reduction, chemical reactions occurring in the target material or products, and the target foil or body may be damaged.

The choice of materials for the target body and entrance foil will depend not only on the strength and chemical stability, but also on the thermal properties. In this next section we will explore some basic principles in heat transfer as they relate to accelerator targets.

From the first law of thermodynamics we can write:

$$E = Q - W$$

where E is the internal energy
Q is the heat
W is the work

Any mode of heat transfer involves a temperature differential as the driving force, and as one might expect, the greater the temperature gradient, the faster the heat transfer will be. There are three modes of heat transfer which are involved to one extent or another in accelerator targetry. These modes are radiation, conduction, and convection.

#### *5.5.1.1. Radiation*

The heat loss by radiation is usually minor, except for target foils or solid targets with low thermal conductivity and high beam current. It is usually assumed in these cases that the heat emitted by the surface is all absorbed in some other part of the beam line or target, and very little is radiated back to the target. The radiative heat loss is the easiest to estimate. If the thermal radiation emitted from a body is thought of as a photon gas, then it is possible to show from thermodynamics that the energy density of the radiation is given by:

$$Q_{rad} = A\sigma T^4$$

where $Q_{rad}$ is the heat emitted as radiation (watts)
A is the area of the surface ($cm^2$)
$\sigma$ is the Stefan-Boltzman constant
T is the absolute temperature (K)

The Stefan Boltzman constant has a value of 9.66 x $10^{-14}$ watt/$cm^2$-$K^4$. This is the amount of heat radiated from a black body into an infinite heat sink. A black body is one in which the absorptivity and emissivity are 1. This is not the case for real objects, but the emissivity and absorptivity are usually equal to one another or:

$$\beta \text{ (emissivity)} = \alpha \text{ (absorbtivity)}$$

This implies that the heat given off by a body at temperature $T_1$ to surroundings of temperature $T_2$ is then:

$$Q_{rad} = A\beta\sigma(T_1 - T_2)^4$$

A very important aspect of radiative heat transfer is the system geometry. When an object is heated as it is with an accelerator beam, radiation is emitted in all directions, and only a fraction of it will actually strike a surface where it can be absorbed and removed. This fraction is called the shape factor, F. The shape factor is defined as the fraction of thermal energy, leaving the surface of object 1 and reaching the surface of object 2, determined entirely from geometrical considerations. Stated in other words, it is the fraction of object 2 visible from the surface of object 1, and ranges from zero to 1. Its units are dimensionless. These shape factors can be calculated using formulas, but the usual method is to look up the shape factors in tables which have been compiled [17]. The values of the heat lost by radiation for a metal with a heated surface area of 3 $cm^2$ (a typical number for the area of a beam spot on the front foil of a cyclotron target) and an emissivity of 0.5 (also typical of metal foils at high temperature) is given in Table 5.

TABLE 5. HEAT LOSS BY RADIATION

| Temp. (°C) | Temp. (°K) | $Q_{rad}$ (watts) |
|---|---|---|
| 100 | 373 | 0.0001 |
| 200 | 473 | 0.0023 |
| 300 | 573 | 0.0117 |
| 400 | 673 | 0.0371 |
| 500 | 773 | 0.0906 |
| 600 | 873 | 0.1878 |
| 700 | 973 | 0.3479 |
| 800 | 1073 | 0.5935 |
| 900 | 1173 | 0.9507 |
| 1000 | 1273 | 1.449 |
| 1100 | 1373 | 2.122 |
| 1200 | 1473 | 3.000 |
| 1300 | 1573 | 4.138 |
| 1400 | 1673 | 7.336 |
| 1500 | 1773 | 9.496 |

It can be seen from this table that the amount of heat eliminated by this process is not significant below about 500°C. Since the amount of heat deposited in a foil can be on the order of 2-40 watts (1MeV x 20 µA to 0.2 MeV x 200µA), it is usually necessary to apply some other method of heat transfer such as convective cooling to the target foil.

#### *5.5.1.2. Conduction*

The second mode of heat transfer is conduction. Conductive heat transfer is extremely important in the design of cyclotron targets, especially in the construction of the target body, since this is where most of the heat from the beam will be deposited.

The heat will be conducted from the hotter region of a material to the cooler region according to Fourier's Law which is in one dimension:

$$Q_{cond} = -kA\ dT/dx$$

where $Q_{cond}$ is the heat transferred by conduction (watts)
A is the cross-sectional area ($cm^2$)
k is the thermal conductivity (watts/cm-°C)
dT is the temperature differential (°C)
dx is the distance differential (cm)

If this equation is integrated holding k, A and q constant, then the result is the heat transfer equation in one dimension given by:

$$Q_{cond} = \frac{-kA(T_1 - T_2)}{x}$$

where k is the coefficient of thermal conductivity (watt/cm-°C)
A is the cross-sectional area ($cm^2$)
x is the distance (cm)
$T_1$ is the temperature of the hotter part (°C)
$T_2$ is the temperature of the cooler part °C)

In the case of a foil where the beam radius is $r_i$ and the foil radius is $r_o$, the steady-state heat transfer from the inner hot area to the outer cooled area is given by:

$$Q_{cond} = -\frac{2\pi kL(T_i - T_o)}{\ln\left(\frac{r_o}{r_i}\right)}$$

where L is the thickness of the foil (cm)
$T_i$ is the temperature of the beam strike area (°C)
$T_o$ is the temperature of the outer radius of the foil °C)
$r_o$ is the foil radius (cm)
$r_i$ is the beam radius (cm)
k is the thermal conductivity (watt/cm-°C)

Several assumptions have been made in this equation. The first is that the thermal conductivity does not change as a function of temperature. The second is that the inner beam strike area is at a uniform temperature. These assumptions are rarely valid, but it does give a place to start in the estimation of the heat dissipated by the different processes. It is also fairly valid in a few specific cases. It is usual, in this situation, to know the power being deposited into the window (which is the beam current times the beam energy lost in the window). The parameter we need to calculate is the temperate of the foil in the beam strike area to determine if the foil will withstand the heat load. In the case of a 0.0254 cm (0.010") thick aluminum foil, the energy deposition of an 18 MeV proton beam in the foil will be 1.35 MeV. At a beam current of 20 μA, the heat load will be 27 watts. The thermal conductivity of aluminum at 300 K is 2.37 watt-$cm^{-1}$-$°K^{-1}$. If the beam spot radius is 0.75 cm and the foil radius is 1.5 cm, then the temperature at the center of the foil is:

$$T_i = \frac{\left[Q_{cond} \ln\left(\frac{r_o}{r_i}\right)\right]}{2\pi kL} + T_0$$

$T_i = (27)(.693)/2\pi(2.37)(.0254) + 300°K = 350°K$

So, this amount of power only raises the temperature of the foil by 50 degrees, well within the boundaries of any significant change in the yield strength of the foil. If the foil is 0.051 cm (0.002") Havar, however, the energy loss will be 0.8 MeV (16 watts at 20 μA) and the temperature of the foil will be:

$T_i = (16)(.693)/2\pi(0.17)(.0051) + 300°K = 2335°K$

This foil temperature is well above the melting point of Havar. The conclusion is that conductive cooling will not be sufficient for low thermal conductivity materials.

#### *5.5.1.3.Convection*

The final mode of heat transfer is convection, which is the most difficult to estimate accurately. The equation for heat transfer is given by:

$Q_{conv} = hA(T_1 - T_2)$

where $Q_{conv}$ is the heat transferred by convection
A is the surface area (cm$^2$)
h is the film coefficient (watt/cm$^2$-K)
T is the temperature (K)

There are two modes of convective heat transfer, free and forced. In free convection, the flow patterns are determined mainly by the buoyant effects of the fluid; whereas in forced convection, the flow pattern is determined by other forces, such as fans or jets. In most cases, the film coefficient for a particular system must be experimentally determined in order to obtain an accurate value.

Some empirical relationships may be used to estimate this quantity for a wide range of situations, which have been tabulated in reference books on heat transfer. The problem in estimating this quantity comes from the boundary layer which exists between a flowing fluid and a stationary solid surface. For example, if a fluid is flowing in a laminar fashion parallel to a sharp edged plate as is shown in Figure 16, a boundary layer is created along the flat plate.

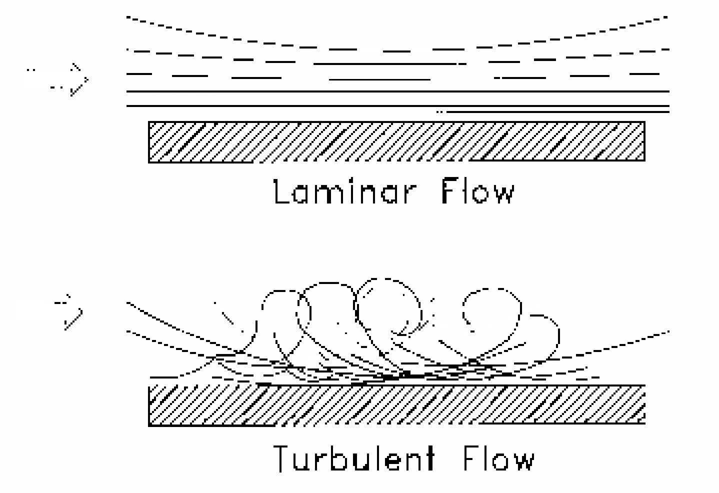

*FIG. 16. Laminar and turbulent flow across a flat plate*

The velocity of the fluid in this boundary layer in close proximity to the surface of the plate is near zero as a result of the viscosity of the fluid. As the fluid flows along the plate, the thickness of the boundary layer will increase. Each lamination in the fluid 'drags' on the layer adjacent to it and causes an increase in the thickness as one proceeds along the plate. The thickness of the boundary layer decreases as the velocity increases. If the fluid and the plate are at different temperatures, then there will also be a thermal boundary layer created. As a consequence of the increasing thickness of this boundary layer, the heat transfer will decrease as the fluid flows over the plate. In the layer nearest the surface of the plate, the heat is transferred nearly entirely by conduction through the fluid. At the next layer, some of the heat is carried away by the flowing fluid and some is transferred by conduction to the next layer and so on, throughout the boundary layer. It should be pointed out that this boundary layer is, in fact, a continuous change in the velocity of the fluid from near zero at the plate to the velocity of the bulk fluid at some distance away from the plate. If there is turbulence in the system, then heat will be transferred much more efficiently by the eddy currents that are created by the turbulent flow.

The characteristics of fluid flow across a surface are often described in terms of several dimensionless parameters. The first of these is the Reynolds Modulus given by the relation:

$$\mathrm{Re} = \frac{xV\rho}{\mu}$$

where Re is the Reynolds number (dimensionless)
V is the velocity of the bulk fluid (cm/sec)
$\rho$ is the fluid density (g/cm$^3$)
$\mu$ is the fluid viscosity (poise (g/cm-sec))
x is the significant dimension (cm)

The Reynolds number represents the ratio of the inertial forces of the fluid to the viscous forces of the fluid. The definition of x needs some explanation.

In certain situations, it is clear what this dimension should be. For example for a fluid flowing inside a tube, the significant dimension would be the diameter of the tube. In a fluid flowing over a flat plate, it is not so easily defined; but if there is a restriction on the thickness of the boundary layer, then this is usually chosen as the significant dimension. The transition from laminar flow to turbulent flow is determined by the Reynolds number. At low Reynolds numbers, the flow is laminar, and at high Reynolds numbers, the flow is turbulent. The transition from one type to the other will depend on a number of factors including the surface roughness and the exact geometry. A good rule of thumb is Reynolds numbers below 1000 represent laminar flow and Reynolds number above 5000 represent turbulent flow. In the transition region between 1000 and 5000 the flow may be either laminar or turbulent, depending on the fluid and the surface. The second dimensionless parameter that is used in convective heat transfer is the Prandtl number given by the expression:

$$\mathrm{Pr} = \frac{C_p\mu}{k}$$

where Pr is the Prandtl number (dimensionless)
$C_p$ is the heat capacity of the fluid (J/g-K)
$\mu$ is the viscosity of the fluid (poise (g/cm-sec))
k is the thermal conductivity (watt/cm-K)

This number represents the ratio of the viscous properties of the fluid to the heat transfer properties. It serves to compare the hydrodynamic boundary layer to the thermal boundary layer. In free convective flow, there is a dimensionless parameter called the Grashof number which is give by the relation:

$$Gr = \frac{L^3 \rho^2 b \beta (T_w - T_b)}{\mu^2}$$

where Gr is the Grashof number (dimensionless)
L is the characteristic length (cm)
$\rho$ is the density of the fluid (g/cm$^3$)
ß is the coefficient of volume expansion (1/K)
g is the gravity constant (cm/sec$^2$)
$\mu$ is the fluid viscosity (poise)
$T_w$ is the wall temperature (K)
$T_b$ is the bulk fluid temperature (K)

This number expresses the ratio between the forces which cause the fluid to have buoyancy, and those forces which tend to retard the fluid flow.

The final parameter to be dealt with in convective heat transfer is the Nusselt number, which is defined in the case of forced convection by the relation:

$$Nu = \frac{hx}{k}$$

where Nu is the Nusselt number (dimensionless)
h is the film coefficient (watt/cm$^2$-K)
x is the significant distance (cm)
k is the thermal conductivity (watt/cm-K)

The Nusselt number has the form of a thermal conductance, and may be thought of as the ratio between the heat transport by convection and the heat transport by conduction through the fluid. This expression contains the term h, which is the number required to determine the heat transfer according to the initial equation. The design equations for the types of convective heat transfer are based, in the most part, on empirical relationships between the Nusselt number and the other dimensionless parameters. For example, the expression for laminar flow in tubes is:

$$\frac{hx}{k} = 1.86(\mathrm{Re})^{1/3}(\mathrm{Pr})^{1/3}\left(\frac{x}{L}\right)^{1/3}\left(\frac{\mu_b}{\mu_w}\right)^{0.14}$$

where x is the tube diameter (cm)
L is the tube length (cm)
$\mu_b$ is the bulk fluid viscosity (poise)
$\mu_w$ is the fluid viscosity at the wall (poise)

In this case, the viscosity at the wall ($\mu_w$) will be approximated by using the viscosity at a temperature, which is the average of the wall temperature and the fluid temperature. If the flow in the tube is turbulent (as defined by the Reynolds number), then the relationship is:

$$\frac{hx}{k} = 0.023(\mathrm{Re})^{0.8}(\mathrm{Pr})^{1/3}\left(\frac{\mu_b}{\mu_w}\right)^{0.14}$$

If the convective heat transfer is free (for example, no forced movement of the fluid past the object), then the Nusselt number is given by the relation:

$$\mathrm{Nu} = 0.61(\mathrm{Gr})^{1/4}(\mathrm{Pr})^{1/4} \quad 10^3 < \mathrm{Gr} < 10^7$$
$$\mathrm{Nu} = 0.73(\mathrm{Gr})^{1/4}(\mathrm{Pr})^{1/4} \quad 10^8 < \mathrm{Gr} < 10^{10}$$

These particular relationships are for flow past a vertical wall which is a common situation in cyclotron targetry, especially the case of water over a plate. A possible flow pattern for the gas inside the target is shown in Figure 17.

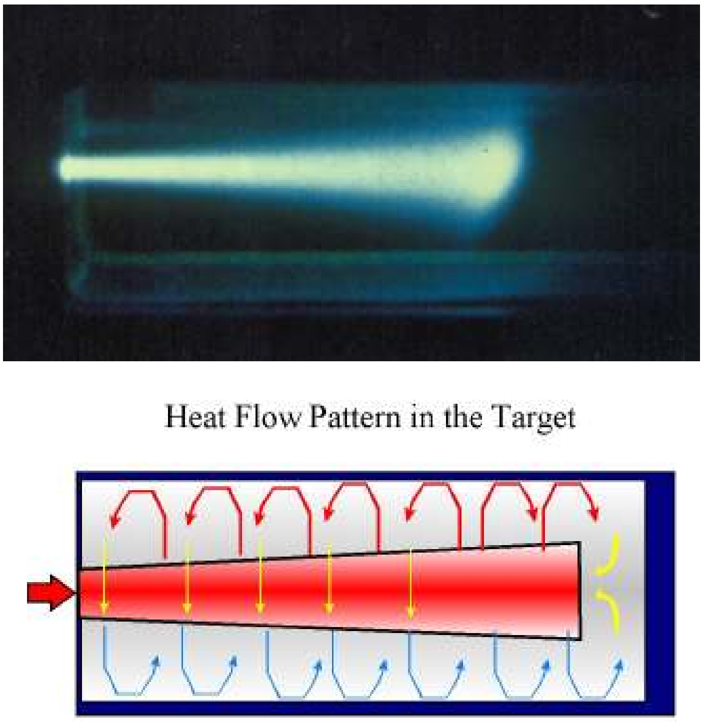
Heat Flow Pattern in the Target

*FIG. 17. Heat flow pattern set up in gas target during irradiation.*

Upper picture is gas during irradiation and flow pattern is shown in lower schematic (photo courtesy of Sven-Johan Heselius).

This diagram shows how the convection currents might be set up in a static target during irradiation [16]. 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.

In cyclotron targetry, it is usual to have both free convection and forced convection. In a gas or liquid target during irradiation, the heating of the fluid inside the target body will set up free convection currents. This flow will aid in removing some heat from the fluid and to decrease the effects of density reduction. It is also usual to have some forced convective flow of gas over the front entrance window and forced flow of water through the target body. For many reasons, the gas used to cool the windows is often helium. Since this gas has a very low viscosity, it is very efficient in cooling the front window (and it does not activate). Some typical values for fluids used in the cooling of windows and target bodies are given in Table 6, along with simplified equations for the various dimensionless parameters.

TABLE 6. HEAT TRANSFER PARAMETERS FOR FLUIDS COMMONLY USED

| Fluid | Temp (°K) | Heat Capacity Cp(J/g-°K) | Thermal Cond. k(mwatt/cm-°K) | Viscosity μ(centipoise) |
|---|---|---|---|---|
| Water | 273 | 4.2177 | 5.65 | 1.787 |

|  |  |  |  |  |
|---|---|---|---|---|
|  | 280 | 4.197 | 5.74 | 1.472 |
|  | 290 | 4.184 | 5.9 | 1.081 |
|  | 300 | 4.179 | 6.04 | 0.8513 |
|  | 320 | 4.1799 | 6.37 | 0.5755 |
|  | 340 | 4.1879 | 6.59 | 0.4213 |
|  | 360 | 4.2023 | 6.75 | 0.3259 |
|  | 373 | 4.216 | 6.83 | 0.2818 |
| Nitrogen | 250 | 0.05833 | 0.19 | 0.01563 |
|  | 284 | ---- | ---- | 0.01707 |
|  | 300 | 0.05886 | 0.2598 | 0.01781 |
|  | 350 | 0.05939 | 0.2939 | 0.01986 |
|  | 400 | 0.05993 | 0.3252 | 0.02191 |
|  | 450 | 0.06046 | 0.3564 | ---- |
|  | 500 | 0.06099 | 0.3864 | 0.02554 |
|  | 572 | ---- | ---- | 0.02791 |
|  | 600 | 0.06206 | 0.441 | ---- |
|  | 763 | ---- | ---- | 0.03374 |

| Fluid | Temp* (°K) | Thermal Cond. k (mwatt/cm-K) | Temp (°K)* | Viscosity μ (centipoise) |
|---|---|---|---|---|
| Helium ‡ | 200 | 1.151 | 273 | 0.01861 |
|  | 300 | 1.499 | 293 | 0.01941 |
|  | 350 | 1.646 | 373 | 0.02281 |
|  | 400 | 1.795 | 473 | 0.02672 |
|  | 450 | 1.947 | 523 | 0.02853 |
|  | 500 | 2.114 | 680 | 0.03436 |
|  | 600 | 2.47 | 879 | 0.04087 |

*In the case of helium, the first temperature in the table is the reference for the thermal conductivity while the second is the reference for the viscosity.

‡The heat capacity for helium is constant at 0.2967 J/g-°K.

Centipoise multiplied by .01 gives units of g/cm-sec.

Milliwatts multiplied by $10^{-3}$ gives J/sec.

Linear interpolation between temperatures, although not completely accurate, gives reasonably good values for the parameters in most cases. If more accurate values are required, they can be obtained from tables and equations in Engineering Handbooks

### *5.5.2 Target Window Foil Materials*

One of the most important components of any target system is the foil through which the beam enters the target material. This component is sometimes absent in solid targets, but is usually required in both liquid and gaseous targets. There are several important parameters in the choice of a foil. Often, the best choice with regard to one parameter will not be the best choice with regard to another parameter, so compromises are often necessary. The important parameters in the choice of a foil are:

- The thermal conductivity
- The tensile strength
- The chemical reactivity (inertness)
- The energy degradation properties
- Radioactive activation
- Melting point

Each of these parameters interacts with the others in some subtle ways. For example, the stopping power will determine the amount of power deposited in the foil, which in combination with the thermal conductivity will set the temperature. The temperature will have an effect on the yield strength of the foil and may affect the chemical reactivity of the foil.

### *5.5.2.1. Thermal Conductivity*

The thermal conductivity of the foil will determine the rate at which heat will be removed from the foil. If the foil is also cooled by either forced or free convection on the front surface (not in a vacuum), the heat deposited by the beam will be removed by a combination of these two processes. Foil materials such as aluminum are very good thermal conductors. The thickness of the foil will also determine the amount of heat which can be removed by this process as is evident from examining the equation for heat transfer by conduction. A list of some common foil materials and the thermal conductivity for each is given in Table 7.

TABLE 7. PHYSICAL AND THERMAL PROPERTIES OF SOME FOIL MATERIALS

| Material | density (g/cm3) | Melt. Pt. (°C) | Tensile St. (kpsi) | Thermal Cond. (watt/cm-°K) | dE/dx (MeV/g/cm$^2$) |
|---|---|---|---|---|---|
| Carbon | 2.2 | >3000 | --- | 2.51 | 41.08 |
| Aluminum | 2.71 | 660 | 30 | 2.37 | 33.96 |
| Titanium | 4.5 | 1668 | 120 | 0.31 | 29.77 |
| 316 Stainless | 8.02 | 1427 | 120 | 0.29 | 28.91 |
| Havar | 8.3 | 1493 | 250 | 0.17 | 28.6 |
| Nickel | 8.9 | 1453 | 120 | 0.91 | 28.53 |
| Tantalum | 16.6 | 2996 | 70 | 0.53 | 18.57 |
| Tungsten | 19.3 | 3387 | 500 | 1.8 | 18.42 |
| Platinum | 21.4 | 1769 | 20 | 0.72 | 18.3 |
| Niobium | 8.57 | 2477 | 40 | 0.54 | |

As can be seen from the table, the thermal conductivity of foil materials varies over a wide range. If the thermal conductivity of a foil material is not sufficient to remove the heat deposited in the foil from the beam, then the convective cooling must be increased to make up the difference.

The back of the foil is usually only cooled with free convection from the circulating target gas or liquid. In some flow-through target designs, however, the target gas is injected through a jet onto the rear of the foil to increase the heat removal. This can be an effective cooling method in gas targets.

As an illustration of the effects that convective cooling can have on the temperature of a foil, a simulation has been carried out and is presented in Table 8. Increasing the film coefficient (h) decreases the temperature of the foil so that it can withstand higher beam currents. Havar was chosen as an example because the thermal conductivity is low which means that convective cooling must be the primary means of heat removal. The blanks in the table means the temperature was above the melting point of Havar at 1493°C.

TABLE 8. FOIL TEMPERATURE AS A FUNCTION OF THE CONVECTIVE FILM COEFFICIENT

| Beam current (μA) | Power density (watts/cm$^2$) | Foil Temperature (°C) | | | |
|---|---|---|---|---|---|
| | | h=0 | h=0.01 | h=0.03 | h=0.06 |
| 20 | 15.3 | --- | 1114 | 484 | 240 |
| 40 | 30.6 | --- | --- | 936 | 491 |
| 60 | 45.8 | --- | --- | 1331 | 735 |
| 80 | 61.1 | --- | --- | --- | 973 |
| 100 | 76.4 | --- | --- | --- | 1199 |

- Parameters: $Q_{conv} = hA(T_2-T_1)$

- Material - Havar
- Ambient Temp. - 300 °K
- Cooling gas (helium) temperature - 260 °K
- Beam diameter - 0.5 cm
- Foil diameter - 2.0 cm
- Emissivity - 0.13
- Thermal conductivity - 0.12 watt/cm-°K
- 16 MeV proton incident beam

Tensile Strength: Another important parameter is the tensile strength of the foil. The stress placed on a circular membrane is given by the relation:

$$\varphi = 0.25\left[\frac{P^2Ea^2}{h^2}\right]^{1/3}$$

where φ is the stress placed on the membrane
P is the pressure (psi)
E is the Young's Modulus (psi)
a is the radius of the foil (cm.)
h is the thickness of the foil (cm.)

If the stress on the foil exceeds the tensile strength of the foil, then the foil will burst. This will usually occur in the center of the foil, since this is where the maximum stress occurs on a well clamped foil (i.e. a clamping flange where edges have been radiused). Some values for the tensile strength of some common foil materials are given in Table 7. The deflection of the foil from the plane of the foil [18] is given by the relation:

$$w = a\left[\frac{Pa}{Eh}\right]^{1/3}$$

where: w is the deflection in cm

The other symbols have the same meaning as in the equation for the stress on the foil.

In addition to these equations which are valid for all circular membranes, there is an empirical relationship for Aluminum 5052-0, which is an alloy often used for targets and target foils. The empirical relationship is:

$P_{max} = 13.8t - [75+63(1-e^{-0.2(x-2)})][0.057t + 0.0042t^2]$ for $x > 2$
$P_{max} = 13.8t - 75(x-1)[0.0575t + 0.00425t^2]$ for $1 < x < 2$
$P_{max} = 55.2\ (t/D)$ for $0 < x < 1$

where $P_{max}$ is the bursting pressure (psi)
D is the diameter (inches)
t is the thickness (0.001 inches)
x is D/4

For stainless steel, the empirical relationship is $P_{ss} = 5.6\ P_{max}$

where $P_{ss}$ is the maximum pressure for 316 stainless steel
$P_{max}$ is the maximum pressure for aluminum 5052-0

In all the above estimations, the calculated values are for room temperature and the maximum stress the foil will withstand decrease with increasing temperature. The temperature dependence of the yield strength can be quite different depending on the material. The yield strength versus stress curves for several materials is given in Figure 18. It can be clearly seen that for most materials, the yield strength decreases rapidly with increasing temperature. This is not the case, however, with certain types of stainless steels, where the yield strength increases slightly before decreasing with increasing temperature. Thus, the pressure in the target and the temperature during irradiation will determine the thickness of the foil which will be necessary to withstand the stress.

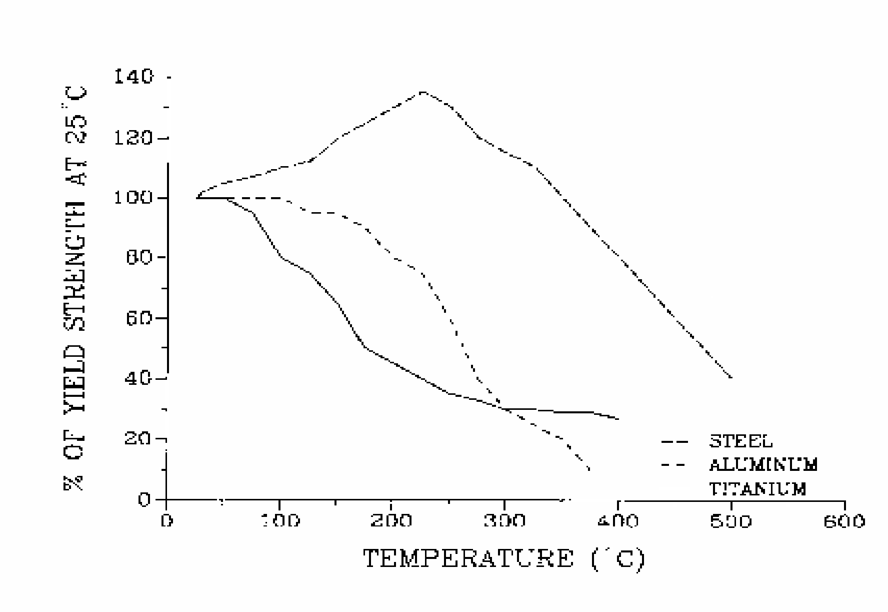

*FIG. 18. Yield strength as a function of temperature for some common foil materials. Yield strength given as the percentage of yield strength at 25°C. See table 8 for absolute values*

### *5.5.2.2. Chemical Reactivity*

The next important characteristic of the foil is the chemical reactivity. This depends on the target material. In nitrogen targets, the foil is often aluminum, since this material is chemically inert to the nitrogen gas and to the carbon-11 products produced.

Aluminum cannot be used in a target for the production of fluorine-18 from oxygen-18 water since the fluorine interacts with the aluminum and it is very difficult to remove the fluorine-18 from the target. An aluminum target can be used for gaseous fluorine-18 production since the surface can be made non-reactive by exposure to fluorine gas at low concentrations. It is necessary to consider the chemical combination of the foil material with the target material not only at room temperature but also at elevated temperatures, since this is often the situation inside the target. Each target must be considered on a case by case basis, and there are no rules other than those of chemistry.

### *5.5.2.3. Energy Degradation*

The energy loss in the foil is another consideration, since this will have an impact on the beam energy incident on the target material and also on the heat which is deposited in the foil. The energy degradation relates to the stopping power of the material as was calculated in the previous section. The ideal situation is to have a foil as thin as possible to withstand the pressure in the target so that the minimum amount of energy is deposited in the foil. An exception to this rule comes up when it is necessary to reduce the beam energy in order to have the energy incident on the target material at an optimum energy with respect to the cross-section of the desired nuclear reaction.

#### *5.5.2.4. Activation of Foils*

Another consideration is the radioactivation of the target foils, since this will often determine how radioactive the target will be. All target foils need to be replaced at fairly frequent intervals and this can result in a radiation dose to the person working on the target. Aluminum is often the material of choice in this regard, because there are very few long lived activities formed in the foil. Nickel alloys and steels, which must be used for chemical inertness in certain situations, are perhaps the worst commonly used materials with respect to activation, since these metals often have several long-lived activities associated with them.

#### *5.5.2.5. Melting Point*

The final item in the list is the melting point. The ideal foil material would have a very high melting point so that heating of the foil by the beam would not be a problem. The most widely used foil is aluminum which has a low melting point. In this case, the other attractive properties of aluminum outweigh the disadvantage of a low melting point.

### 5.5.3 Target Body Materials

There are five important characteristics for target body materials. These are:

- Thermal conductivity
- Chemical reactivity
- Activation
- Ease of machining/manufacture
- Mechanical strength

These characteristics share nearly equal importance in the choice of a material for target body. Samples of common materials used in target body construction along with some values for the five characteristics are given in Table 9.

The most common material for the construction of target bodies is aluminum. It has a high thermal conductivity, activation products which have short half-lives or are not made in great abundance, is chemically inert to most gases under irradiation conditions, and is easily machined. The disadvantage is that it is difficult to weld to other materials.

TABLE 9. PHYSICAL AND THERMAL PROPERTIES OF SOME TARGET BODY MATERIALS

| Material | Thermal Conductivity (watts/cm °C) | Chemical Reactivity | Nuclear Activation | Ease of Machining | Tensile Strength, kpsi |
|---|---|---|---|---|---|
| Aluminum | 2.37 | good | p - negligible<br>d - $^{24}$Na | good | 110 |
| Aluminum 3003 | 2.63 | good | | | 130 |
| Aluminum 6061 | 1.80 | good | | | 115 |
| Copper | 4.03 | fair | p - $^{65}$Zn, $^{62}$Zn, $^{64}$Cu<br>d - $^{65}$Zn | excellent | 344 |
| Nickel | 0.91 | excellent | p - $^{57}$Ni, $^{55}$Co<br>d - $^{64}$Cu | good | 175 |
| Monel | 0.32 | excellent | same as nickel | good | 112 |
| Silver | 4.27 | good | p,d - $^{107}$Cd, $^{109}$Cd | good | 170 |
| Titanium | 0.31 | excellent | p - $^{48}$V | good | 300 |

| | | | | | |
|---|---|---|---|---|---|
| | | | d - $^{49}V$ | | |
| Stainless Steel | 0.29 | good | p - $^{56}Co$, $^{55}Co$<br>d - $^{57}Co$, $^{56}Co$ | good | 860 |
| Brass | 2.01 | fair | same as copper | | 250 |
| Niobium | 0.54 | excellent | | good | 300 |

The thermal conductivity of the target body is important since the heat, which is generated inside the target, must be transferred through the target body material to a heat sink. The normal method of heat dissipation is water cooling. The number of cooling channels, the distance between inner wall and water cooling channel, and the way in which the water cooling channels are cut, determines the heat transfer from the metal target body to the water. Increasing the surface area between the water and the metal body (assuming similar Reynolds number) increases the heat transfer as was shown in the section on convective heat transfer. The use of fins to increase surface area as well as parallel water channels have been used in high heat load targets. In some cases it is not possible to use water for cooling. In some situations, other liquids or gases must be used.

The chemical reactivity of the target body material is significant particularly if the material retains the radioisotope chemically [19]. This can be used to advantage if the radioisotope can be easily removed with washing or some other chemical dissolution. The chemical compatibility is more important with solid and liquid targets, since the reactive material is more concentrated. The activation of the target body is an obvious consideration when the time comes to repair or maintain the target. This may be the deciding factor in whether to build a duplicate target which can be put into service while the radioactivity in the other target is allowed to decay.

Machining is a consideration even when a high quality machine shop is available to do the fabrication. The cost of any target will depend, to a great extent, on the time required to machine it. The compatibility of materials will enter into this category also. If welding, brazing or soldering must be used, the materials (solders and fluxes) used must be compatible with the target material. Some target designers have begun using Electric Discharge Machining (EDM) to form target bodies. This method uses no organic solvents or cutting oils. This, in turn, can significantly decrease contamination with targets such as the carbon-11 target where specific activity is so important.

In general, any use of cutting lubricants should be avoided, unless well established cleaning procedures are available. Ultrasound baths may be used to remove solvents. The use of all metal O-rings or C-rings is recommended.

### 5.5.4. Power Density with Inclined Planes

As has been discussed in previous sections, one of the more difficult problems in accelerator targetry is dissipation of the heat generated as the beam passes through the absorber. One approach, often taken with solid targets, is to use the inclined plane to spread the beam out over a larger area and thereby reduce the power density in the beam strike area. This can be accomplished relatively easily on internal targets by inclining the target to the beam and bending the target plate to the curvature of the beam in the outer orbits of the cyclotron. An example of this is given in Figure 19.

The difference in beam profile can be seen easily in the following beam profiles. The first is using a flat plate at a grazing incidence of a few degrees. The second is a plate that has been shaped by hand to approximate the curvature of the beam in the outer orbits. The third is the beam strike profile when the target plate has been optimized to match the exact curvature of the beam.

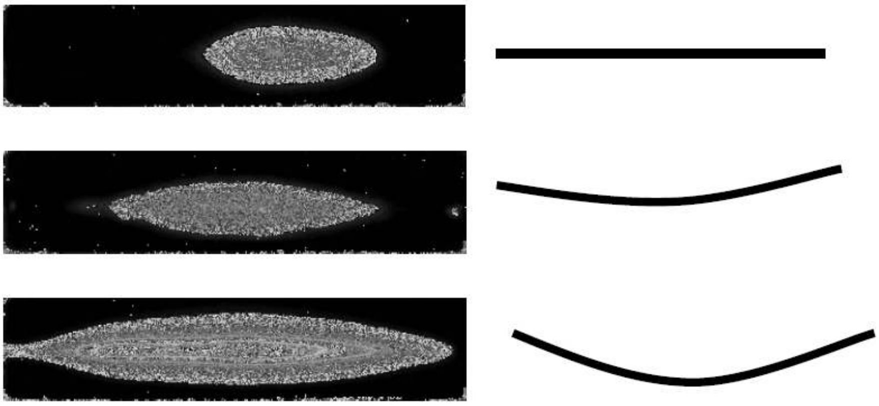

*FIG. 19. Beam profile of internal target beams on plates of various shapes. The closer the plate matches the beam curvature, the better the distribution of the beam along the plate*

Inclined planes may also be used on external targets. A simple example of this type of target is given in Figure 20.

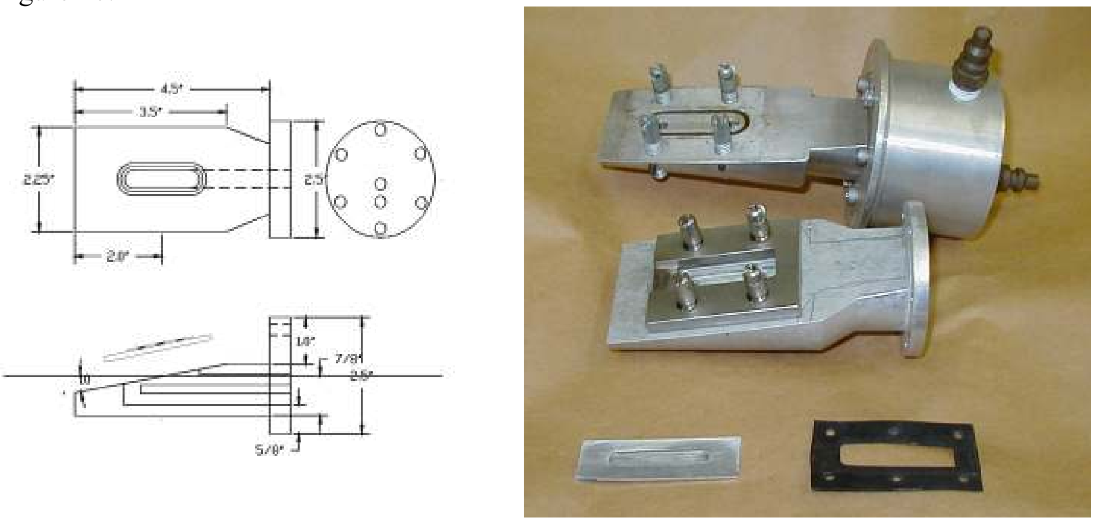

*FIG. 20. Example of inclined plane external target used for solid materials either pressed or melted into the depression in the target plate*

## 5.6 BEAM TRANSPORT

The extracted beam is often transported from the accelerator to the target by the beam transport system. This can be a series of dipole and quadrupole magnets, magnetic lenses, collimators and beam monitors, or as in the case of many small cyclotrons where the targets are attached directly to the machine, it is just a beam collimator. The arrangement of magnets, vacuum chambers, and diagnostic instrumentation is called a beam line. The beam transport system modifies and monitors the beam to achieve the optimum beam distribution inside the target volume. The ease of adjusting the beam through the beam line (tuning the beam line) and the reproducibility of the beam-line tune are critical for efficient and reliable radioisotope production. Beam tuning means adjusting the beam optics to transport the beam to the desired location with the desired shape and intensity at that location.

### 5.6.1 Collimators

Collimators are usually designed to be slightly smaller than the target opening or window. This is important for two reasons. First the size of the beam is limited to the size of the target opening and, therefore, the beam current that is read on the target is an accurate indication of the beam hitting the target; and second, it prevents the front flange of the target from becoming activated and therefore lowers the radiation dose to the operator when maintenance is required. The ideal collimator is divided into several sectors which may be monitored independently. This allows the beam to be steered to obtain the maximum beam current on the target more efficiently.

### 5.6.2 Beam Focusing

The beam exiting an accelerator can have unusual shapes depending on the dynamics of the acceleration and extraction as well as on the fringing field in cyclotrons. It is sometimes desirable to focus the beam with quadrupole magnets. This also allows some smoothing of the beam in those accelerators where the beam may have some 'hot spots', or spikes in the intensity profile.

### 5.6.3 Wobbling and Rastering

The purpose of wobbling or rastering the beam is to lower the power density on the target. This in turn allows the target to be operated at higher beam currents with the resulting higher yields of radioisotope production. It is necessary to have a beam line of some sort in order to take advantage of this method of power dissipation. These dynamic beam delivery systems (wobblers or scanners) are developed to overcome the undesirable necessity of scattering materials in the beam and, therefore, lowering the energy.

### 5.6.4 Beam Profile Monitoring

Beam lines are often equipped with beam profile monitors. These devices monitor the shape of the beam usually in two dimensions. They allow the operator to adjust the beam shape with steering and focusing magnets to get the ideal beam shape on target. There are many different designs of beam scanners from simple wires, which can be inserted in the beam to more sophisticated scanners which give fine resolution images of the beam shape with a rotating wire attached to an oscilloscope.

## 5.7 ENRICHED MATERIALS IN TARGETS

For many years, enriched stable isotopes have been the foundation for the production of isotopically pure radionuclides. In the past decade there has been a significant increase in the acquisition and use of 'small' cyclotrons devoted principally to the production of the radiolabeled compounds or radiopharmaceutical drugs required for biomedical research. The availability and the application of stable enriched target materials for the production of the biologically equivalent radionuclides is of paramount concern, given the energy constraints typical of the various accelerators chosen for installation into imaging facilities.

### 5.7.1 Natural Abundance or Isotopically Enriched Materials

There are two major reasons to use targets that have been enriched in a particular isotope. First, the target may use isotopically enriched material in order to produce more of the isotopes of interest. Second, the use of the natural abundance target element often results in the production of unwanted side products. A simple example involves using O-18 labeled water for F-18 production. The abundance of oxygen-18 in natural oxygen is about 0.2%. This means that using natural abundance water for the production of fluorine-18 would not only produce very little fluorine-18, but would produce much larger quantities of nitrogen-13. It is necessary to use water isotopically enriched in O-18 for the production of F-18.

### 5.7.2 Availability of Enriched Isotopes

The major difficulty with using enriched materials is that they can be very expensive and they may be unavailable at times. This is due to the extensive separations, which are often necessary to produce highly enriched isotopes from a low abundance starting material. For this reason, the isotopically enriched materials need to be recovered after each use and reused. This can require involved chemistry and great care in separation and purification to ensure the chemical and isotopic purity of the target material.

## 5.8 TWO SIMPLE EXAMPLES: SOLID TARGET FOR Tl-201 AND GAS TARGET FOR C-11 PRODUCTION

The purpose of this section is to give some very simple examples of the application of the formulas and suggestions contained in this chapter. The examples are for the production of thallium-201 using a solid thallium-203 target, and the design of a gas target for the production of carbon-11 from nitrogen gas.

### 5.8.1 Solid Target for Tl-201 Production

The first step in the design of the target is to decide the optimum energy interval for a particular nuclear reaction. The nuclear reaction used for the production of $^{201}$Tl is the $^{203}$Tl(p,3n)$^{201}$Pb reaction. The Pb-201 ($T_{1/2}$ = 9.33 hours) produced in the reaction is then allowed to decay to $^{201}$Tl ($T_{1/2}$ = 76.03 hours) in a separate column. In this case, there are two competing nuclear reactions which is typical of reactions, which evaporate more than one neutron from the nucleus. The data for the nuclear reaction cross sections can be found in the literature and many nuclear reaction cross sections can be found online at the National Nuclear Data Center (http://www.nndc.bnl.gov/index.jsp). The graph of the competing cross sections is shown in Figure 21.

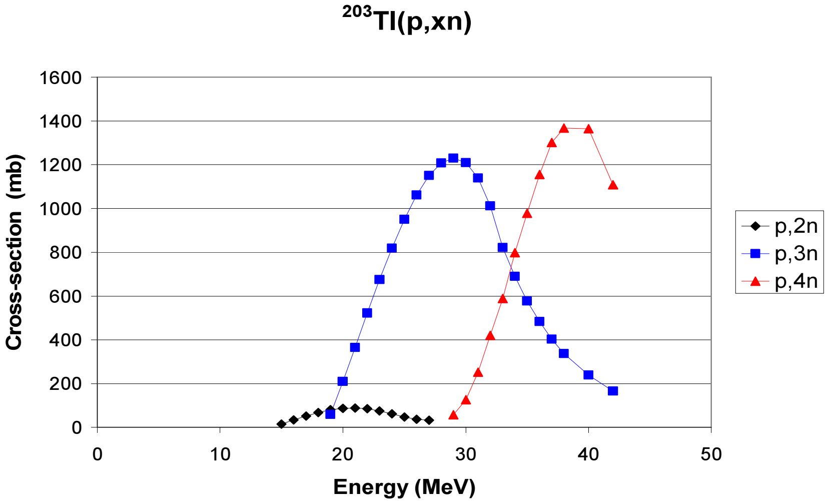

*FIG. 21. Cross Section versus energy plot for the $^{203}$Tl(p,2n)$^{202}$Pb, $^{203}$Tl(p,3n)$^{201}$Pb and $^{203}$Tl(p,4n)$^{200}$Pb nuclear reactions*

From the graph we see that at energies greater than 30 MeV, the production of Pb-200 starts to become significant. At energies less than 20 MeV, the production of Tl-201 drops to very low levels. Therefore, the best energy interval to maximize yields and minimize impurities is over the interval of 20 to 30 MeV.

The target itself will be a thin layer of thallium electroplated onto a copper plate. Copper is chosen because it is relatively easy to electroplate the thallium onto the copper; and copper has an excellent thermal conductivity, which is important in order to remove the heat from the thallium. In back of the copper plate is a water cooling stream to convectively transfer the heat. There are several important parameters for these materials which are listed in Table 10.

TABLE 10. SOME PROPERTIES OF COPPER AND THALLIUM

| Element | Density | Melting Point | Thermal Cond. |
|---|---|---|---|
| Copper | 8.96 g/cm$^3$ | 1083°C | 4.03 W/cm-°K |
| Thallium | 11.85 g/cm$^3$ | 303°C | 0.46 W/cm-°K |

The next step is to calculate the thickness of the thallium layer. The range of protons can be determined from the SRIM code referenced earlier in this chapter. The range of a 30 MeV proton in thallium-203 is 1.75 mm. The range of a 20 MeV proton is 0.89 mm. So, the depth of thallium needed to degrade 30 MeV protons to 20 MeV is 0.86 mm (1.75-0.89). In a similar fashion, to degrade the 20 MeV protons to 0 MeV, 0.8 mm of copper is required. In order to make the copper plate mechanically stable, the thickness will be set at 2 mm.

In order to make sufficient $^{201}$Tl in a reasonable amount of time (based on the cross section, time and saturation factor), a beam current of about 50μA is needed. This means that the total power deposited in the target is 1500 watts (30 MeV x 50μA). In order to explore the efficiency of cooling the copper plate, a proposed design need to be set up and see if it will work. A preliminary design is shown in Figure 22.

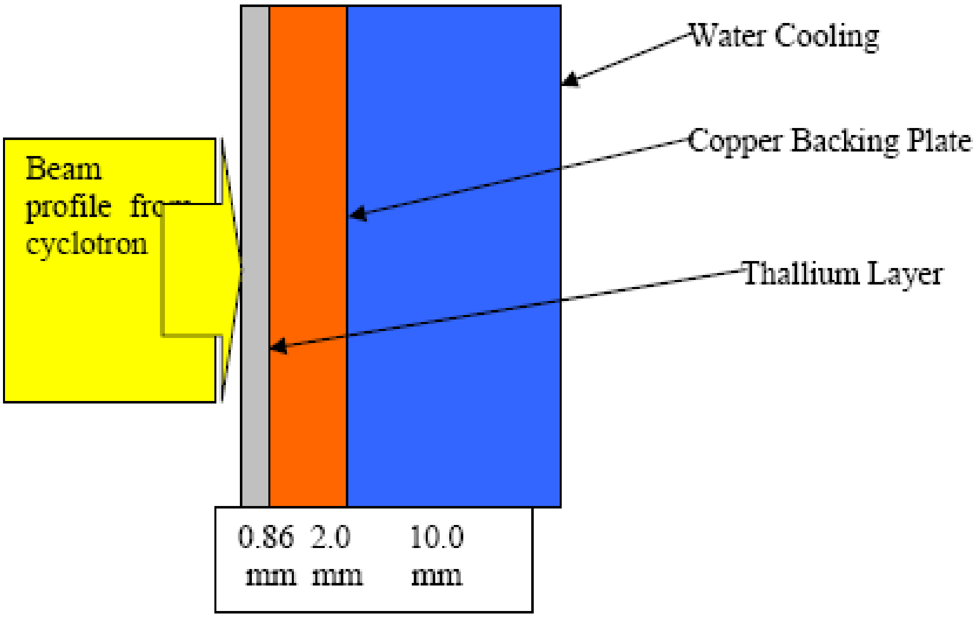

*FIG. 22. Preliminary design of solid thallium target*

The cyclotron beam profile is assumed to be uniform (not usually true) and to have a diameter of 1 cm. The first step is to determine if it is possible to remove the heat in this configuration. We can use the convective heat transfer equation to determine the required film coefficient. The area of the cooling will be slightly larger than the beam profile. The beam area is 0.78 cm$^2$ so we will assume that the cooling area is 1 cm$^2$. We would like to keep the temperature of the plate well below the melting point of thallium, so we can set the $T_2$ at a value of 200°C. The temperature of the water is assumed to be 20°C.

$$Q_{conv} = hA(T_1\text{-}T_2) \quad \text{or} \quad h = Q/A(T_1\text{-}T_2)$$

$$h = 1500 \text{ watts}/(1 \text{ cm}^2)(200\text{-}20°\text{C}) = 8.3 \text{ watts/cm}^2\text{-}°\text{C}$$

It is possible to set the Nusselt number based on this value

$Nu = \frac{hx}{k}$ or Nu = (8.3watts/cm$^2$-°C) x (1 cm)/ (0.00593 watt/cm-°C)
Nu = 1400

If we assume that the flow is over a flat plate we can use the formula for the Nusselt parameter of

Nu = 0.332 Re$^{1/2}$ Pr$^{1/2}$

The Prandlt number is given by:

$$\Pr = \frac{C_p \mu}{k}$$

for water at 290 K, this becomes
Pr = (4.179 J/g-K) x (0.008513 g/cm-sec)/(.00604 watt/cm-K), or
Pr = 5.89

Therefore, the Reynolds number must be:

Re$^{1/2}$ = Nu/(0.332)x(Pr$^{1/2}$) = 1400/(0.332)x(2.43) = 1737
Re = 3.02 x 10$^6$

This is a turbulent flow. The Reynolds number is given by the relation:

$$\mathrm{Re} = \frac{xV\rho}{\mu}$$

If we assume the critical dimension x is 1 cm, then we can calculate the velocity of the water necessary to cool the target

.

V = Reμ/xρ = (3.02 x 10$^6$ )(0.008513 g/cm-sec)/(1 cm)(1.0 g/cm$^3$)
V = 2.6 x 10$^4$ cm/sec

If we assume that the inside of the target cooling volume is 0.5 cm by 2 cm, then the volume of water that must be pumped through the target has to be:

Volume = (2.6 x 10$^4$ cm/sec) (1 cm$^2$) = 2.6 x 10$^4$ cm$^3$/sec = 26 liters/sec.

This is an unreasonable amount of water flow. There are several things that can be done to improve the heat transfer such as reducing the volume of the cooling water chamber to increase flow velocity, or to increase the surface area being cooled by inclining the target to the beam.

There is another parameter which we have not considered, and that is the heat transfer from the thallium layer through the copper plate to the water. This is a conductive heat transfer problem, and the equation for the transfer is given by the relation:

$$Q_{cond} = \frac{-kA(T_1 - T_2)}{x}$$

The heat transfer can also be thought of as:

$$Q = \frac{T_i - T_f}{R_{total}}$$

In analogy to electrical resistance to flow, the total resistance is the sum of the individual resistances. In this case there are two metals. As a first approximation, we can assume that all the heat has to travel through the copper plate. We then have

$T_1$-$T_2$ = Qx/kA = (1500 watts)(0.2cm)/(4.03 watt/cm-°K)(1 $cm^2$)
$T_1$-$T_2$ = 74°K

So there is no problem with the heat transfer through the copper plate. It will easily accommodate the power density.

For the thallium layer it is necessary to pass 500 watts through the layer, but it will be deposited throughout the layer. As an approximation for this, we can assume that 500 watts is being deposited half way through the layer. We will apply the same analysis.

$T_1$-$T_2$ = Qx/kA = (500 watts)(0.043cm)/(0.46 watt/cm-°K)(1 $cm^2$)
$T_1$-$T_2$ = 47 °K

Even if we assume the power has to be transferred through the whole layer, then the temperature differential will only be 94°K. It can be seen that the limiting factor in this target is the water cooling on the back of the target. If we increase the cooling surface area by a factor of five and increase the flow velocity by a factor of five, then the flow can be reduced from 26 L/sec to about 1 L/sec. A much more rigorous evaluation of these parameters is given in Chapter 6.

### 5.8.2 Gaseous Target for $^{11}C$ Production

The first step is to determine the energy interval for the production of carbon-11 from the $^{14}N(p,\alpha)^{11}C$ nuclear reaction. Here there are no real competing reactions so that we can explore the whole energy interval for radioisotope production. The cross section for the production of $^{11}C$ from the reaction on nitrogen is shown in Figure 23.

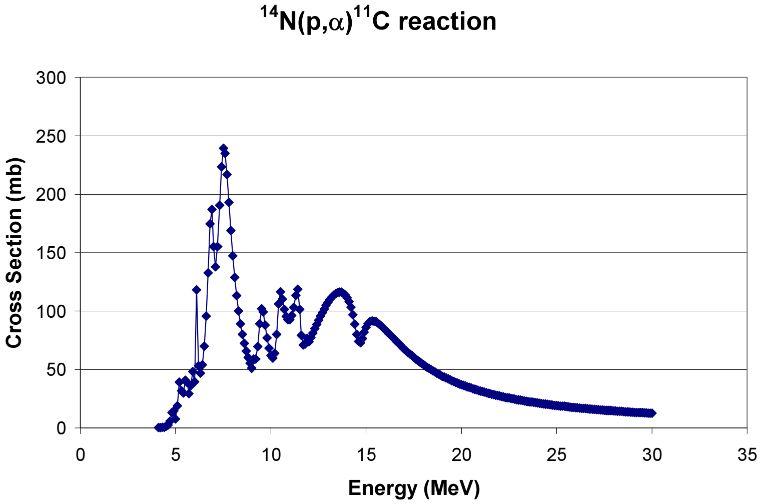

*FIG. 23. Cross section for the $^{14}N(p,\alpha)^{11}C$ nuclear reaction*

It can be seen that the optimum energy for this reaction is between 4 MeV and 20 MeV. The cross section drops off beyond about 15 MeV.

Since many of the cyclotrons that are used for PET have energies of about 17 MeV, we will assume that the entrance energy will be 17 MeV and we want the energy incident on the gas to be at least 15 MeV. The range of a 15 MeV proton in nitrogen gas at atmospheric pressure is 2.31 meters. The pressure inside the target needs to be increased in order to make it a reasonable length. We need to calculate the maximum pressure which can be held by the front foil of the target. If an aluminum front foil is used and we can afford to lose 2.0 MeV of energy in the foil, then the foil can be:

Range 17.0 MeV proton = 1.58 mm
Range 15.0 MeV proton = 1.27 mm
Thickness of aluminum foil = 0.31 mm

For this foil thickness, we can use the empirical relationship for aluminum. We will assume that the foil is 2.54 cm in diameter (1 inch). Thus:

$P_{max} = 55.2\ (t/D)$ for $0 < x < 1$

Here the thickness in thousands of an inch is

(0.31 mm/25.4 mm/in) x 1000 = 12.2 mils, or
$P_{max} = 55.2\ (12.2/1) = 671$ psi or 45 atmospheres

This is the pressure with the beam on. It is also obvious that the yield strength of the aluminum decreases with increasing temperature, so we need to estimate the temperature of the foil, and the pressure inside the target during irradiation. Since the major heat transfer mode will be conduction, the temperature in the center of the foil will be directly related to the beam current on the target. We will make the assumption of a 30 μA beam current, giving a power of 60 watts (2 MeV and 30μA) in the front foil. A first order estimate of the foil temperature can be obtained by doing a simple calculation, using the diagram shown in Figure 24.

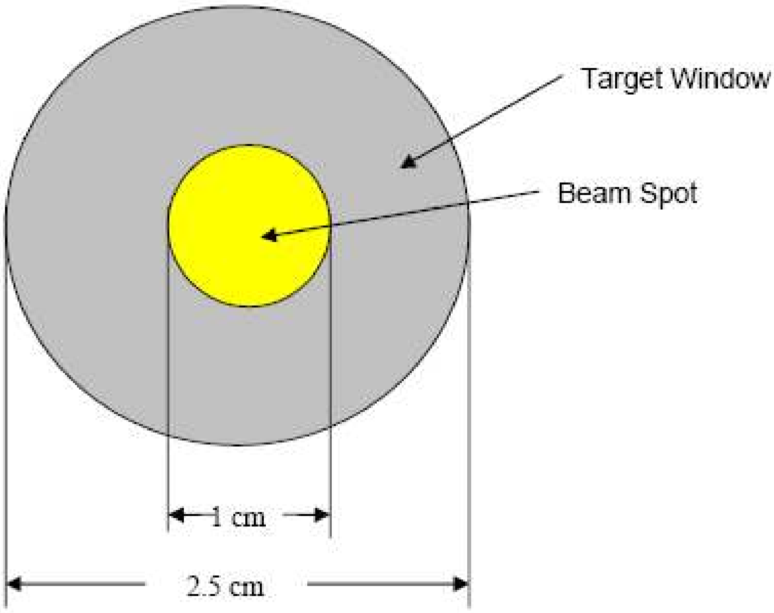

*FIG. 24. Diagram of beam spot on front entrance window of gas target*

We can assume a thermal conductivity of the aluminum of 2.37 watt/cm-°C. The surface area for heat transfer can be assumed as the cross sectional area of the foil at the edge of the beam spot. The distance the heat has to travel to the heat sink is the distance from the edge of the foil to the outer flange. This is given by:

$A = \pi D \times \text{thickness} = (3.14159)(1\text{ cm})(.031\text{ cm}) = 0.097\text{ cm}^2$

The distance the heat has to travel is 1.25 cm – 0.5 cm = 0.75 cm, giving the final relationship:

$T_1\text{-}T_2 = Q\ x/kA = (60\text{ watts})(0.75\text{ cm})/(2.37\text{watt/cm-°C})(\ 0.097\text{ cm}^2)$
$\Delta T = 183°C$

If we assume that the ambient temperature is 20°C and the outer flange is an infinite heat sink, then the temperature at the center of the foil will be about 200°C. If we assume a worse case scenario, then the distance the heat has to travel is from the exact center of the foil to the flange, the temperature differential will be 305°C with a maximum temperature of about 325°C. Looking at Figure 15, we can see that the yield strength is about one third of the strength at room temperature. This means that one can't run the target above about 15 atmospheres. A more exact analysis of the foil temperature gives a temperature in the center of the foil of 201°C, which means the crude estimate was very reasonable. The yield strength at 200°C is close to that at room temperature. In a conservative way, then the pressure in the target will be limited to 15 atmospheres. Since the proton beam will travel through 2.31 meters of nitrogen gas at standard temperature and pressure, at 15 atmospheres 15 cm of gas is needed to stop the beam. Because the beam will be thinned by heating during the irradiation, the estimated length is 20 cm for the target.

It is necessary to calculate the other dimensions of the target. The usual method is to make a conical target since this minimizes the volume of gas used. It is assumed that an aluminum target body will be used as most carbon targets today are constructed of aluminum. It is necessary to avoid hitting the side of the target with the beam since this can reduce the specific activity of the final product. The angle of the beam coming out of the foil into the target needs to be calculated. There is also scattering in the gas, but can be ignored for the moment. The scattering in the front foil is given by the relation (see section 5.3.4):

$$\sigma^2 = 0.0536\left[\frac{xZ^2z^2\ln\left(\frac{3.67\times10^4 E}{zZ^{4/3}}\right)}{AE^2}\right]$$

$\sigma^2 = 0.0536\ (.084*13^2*1^2 \ln[(3.67 \text{ x } 10^4*16/1*13^{4/3})]/27*16^2$
$\sigma = 0.0329$ radians = 1.67°

Since the target is 20 cm long, the distribution of the beam at 20 cm from the front foil can be calculated to determine the geometry of the target. The sigma of the distribution at 20 cm corresponds to a distance of 0.58 cm. A flat distribution beam shape of the proper dimensions (1cm diameter) can be used to estimate the distribution at the back of the target. The rear of the target will be made 3 cm in diameter and the beam distribution at the rear of the target is shown in Figure 25.

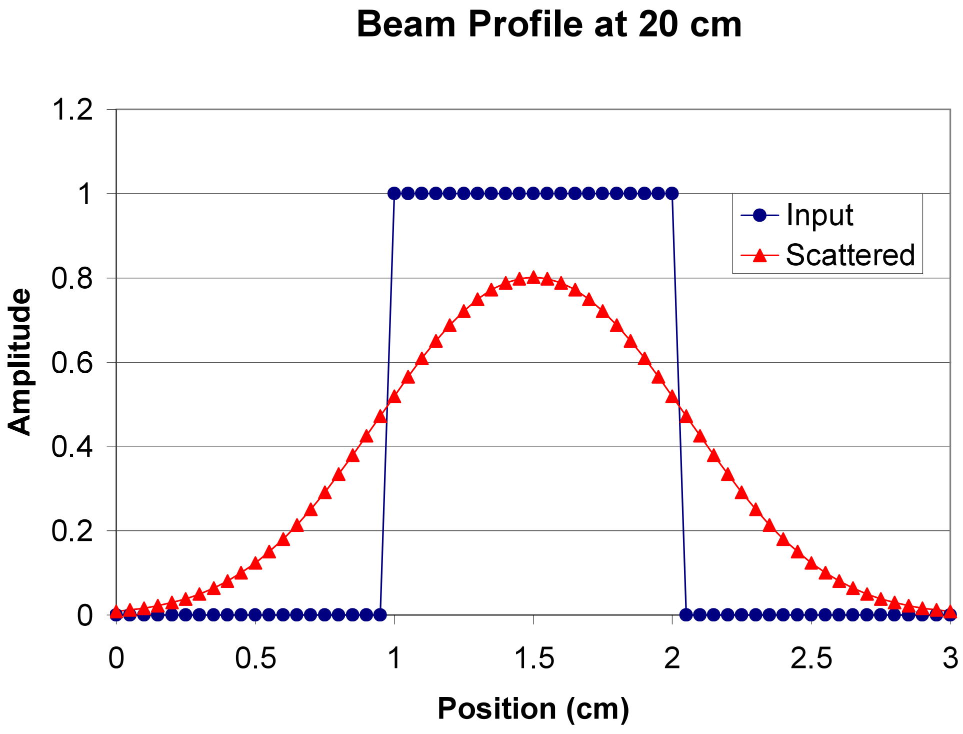

*FIG. 25. Distribution of beam before and after being scattered by the 0.031cm aluminum foil at a distance of 20 cm from the foil.*

It can be seen that a target with a diameter of 3 cm at the back of the target will accommodate the beam. With this a basic volume for the target can be designed. Uncertainty in beam diameter and beam position, may dictate that we increase the diameter slightly.

## 5.9 CONCLUSION

Simple rules and formulas can be used to design new targets for cyclotrons and to help someone unfamiliar with cyclotron targetry to appreciate the interplay of forces [20]. More sophisticated descriptions or computer simulations can be used to advantage, but these quick calculations can be used to compare to the results to ensure that the problem is well described and the results are reasonable.

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# 6 TARGET PREPARATION AND IRRADIATION

## 6.1 INTRODUCTION

The care of targets is one of the prime considerations in maintaining good production yields and ensuring the longest useful lifetime. It is also important in attaining high specific activity radioisotopes. The first section of this chapter examines the preparation, routine maintenance, and care of gas and liquid targets. The remainder of the chapter will focus on the preparation and analysis of solid targets since this is a much more complex matter.

## 6.2 PREPARATION OF GAS AND LIQUID TARGETS

The preparation of gas and liquid targets is generally less labor intensive than the preparation of solid targets. There are, however, a few examples where some significant preparation of gas targets is required [1, 2]. One of these is in the cleaning of the target. Certainly before first use and at regular intervals afterwards, the target needs to be cleaned. For liquid targets, a routine maintenance procedure is also recommended, especially for targets made from certain metals such as silver. In the following sections, some guidelines for the initial fabrication and maintenance of both gas and liquid targets are discussed.

### 6.2.1 Initial Fabrication of Gas Targets

If specific activity is a concern with gas targets, there are some fabrication techniques and cleaning procedures which may be used to reduce the amount of carrier present in the target. One prime example is the target for the production of carbon-11. In this target, it is essential that carbon be kept out of the target. For this reason, the technique of electric discharge machining (EDM) is recommended. This process can be carried out in aqueous solution and eliminates the necessity for cutting oils in fabricating the target. Once the machining is done, the surface is rather rough and can be polished using aluminum oxide grit. Silicon carbide should never be used as this may introduce carbon into the surface of the metal. If EDM is not available, then extensive cleaning after the machining will be necessary using organic solvents or detergents to remove the oil and then washing with water repeatedly to remove the solvents. Cutting oils should be avoided if at all possible.

### 6.2.2 Cleaning of Gas Targets

The use of organic solvents should be kept to a minimum when cleaning the target, and only with extensive washing with water after their use. Ethanol and acetone are preferred as they are soluble in water and can be washed out more easily. If immiscible organic solvents such as hexane are used, there should be a rinse with a solvent miscible with both hexane and water such as acetone. It has been our experience that carbon targets essentially never need to be cleaned, unless there is some accidental introduction of some foreign material into the target. Carbon-11 production targets can also be rejuvenated by irradiating a mixture of 10% oxygen in neon for a short time and then removing this mixture completely from the target before filling the target with the normal nitrogen gas for irradiation. This step is often referred to as a “burn-out.” Fluorine gas targets can be passivated using a similar procedure with 1% fluorine in neon or argon [3].

### 6.2.3 Initial Fabrication of Water Targets

Water targets for the preparation of fluorine-18 should be fabricated without soldering or brazing the connections if possible. The flux commonly used in soldering usually contains boric oxide which is high in fluoride. This fluoride can leach into the water during irradiation and decrease the specific activity of the fluorine-18. There are many designs of water targets which are in current use [4-7] and new designs are constantly being put into routine production. The best source for new concenpts and designs are the Proceedings of the Workshop on Targets and Target Chemistry which are archived at http://trshare.triumf.ca/~buckley/wttc/proceedings.html

### 6.2.4 Maintenance of Water Targets

A suggested frequency and procedure for the cleaning of water targets is given in table 1. This is a general outline and the procedures used should be discussed with the manufacturer of the target to agree on the final procedure. The procedures listed here have been used by several labs with good results. Further information on target care and maintenance can be found in the proceedings of the Targetry Workshops (http://www.triumf.ca/wttc/proceedings.html).

The procedure used and frequency of cleaning depends on the material of construction and the total number of microamp hours on the target. There is no doubt that the target requiring the highest maintenance is the silver target.

TABLE 1. RECOMMENDED CLEANING PROCEDURES FOR WATER TARGETS USED FOR PRODUCTION OF FLUORINE-18

| Material | Frequency | Recommended Procedure |
|---|---|---|
| Silver | 3 to 6 months | Open the target and remove the front foil. Discard this in a shielded container for decay. Remove all O-rings or C-rings depending on the design. Scrub the exposed surfaces with an abrasive pad or with very fine abrasive paper. In extreme cases, it may be necessary to take the pits out of the surface with a high speed mechanical wire brush (Dremel tool). Care should be taken that no fine particles are lodged in the entrance and exit channels. The target should be finally rinsed with copious water, remembering that the water and all other wastes will contain Cd-109 radioactivity and should be disposed of properly as radiological waste. |
| Titanium | 6 months to 1 year | The procedure is very similar to the silver target except that the metal is harder, and a harder abrasive is usually required. The radioactive isotope present in the wash water will be V-48 |
| Niobium | 1 to 2 years | Procedure is the same as for the titanium target. |

### 6.2.5 Cleaning and Polishing of Metal Surfaces

It is often difficult to get inside a target body to polish the surface after cleaning with an abrasive tool. There are a few procedures for the chemical polishing of metal surfaces which have been used to prepare cyclotron targets. After these procedures are carried out, the target body should be thoroughly cleaned with water to remove any traces of the chemicals used in the procedures. These procedures must be followed exactly in order to get a polished surface. Any deviation from the reagent concentrations, temperatures, or times may result in an undesirable finish, which could affect target performance. Testing of the procedures on scrap metals is highly encouraged until reliable results are obtained. The procedures of polishing are given in Table 2.

TABLE 2. CHEMICAL POLISHING PROCEDURES FOR SOME METALS

| Metal | Reagent | Volume (mL) | Time | Temp. (°C) |
|---|---|---|---|---|
| Copper-Zinc alloys | Fuming nitric acid | 80 | 5 sec. | 40 |
| | Water | 20 | | |
| | Use periods of 5 seconds immersion followed immediately by washing in a rapid stream of water. Slight variations in the composition are needed for some alloys to prevent differential attack. With some alloys, a dull film can form which can be removed by immersion in a saturated solution of chromic acid in fuming nitric acid for a few second washing. | | | |
| Irons and Steels | Distilled water | 80 | 15 secs. | 35 |
| | Oxalic acid (100g/L) | 28 | | |
| | Hydrogen peroxide (30%) | 4 | | |
| | The solution must be prepared freshly before use. Careful washing is necessary before treatment. A micro-surface is obtained similar to that produced by mechanical polishing, followed by etching with Nital. | | | |
| Nickel | Nitric acid (Conc.) | 30 | 1 min. | 85-95 |
| | Sulfuric acid (Conc.) | 10 | | |
| | Ortho-phosphoric acid | 10 | | |
| | Glacial acetic acid | 30 | | |
| | This solution gives a very good polish. The temperature is critical. | | | |
| Tantalum | Sulfuric acid | 50 | 5-10 secs. | 20 |
| | Nitric acid | 20 | | |
| | Hydrofluoric acid | 20 | | |
| | Solution is useful for preparing surfaces prior to anodizing. Extreme care must be taken in handling HF | | | |
| Titanium | Hydrofluoric acid (100 Vol.) | 8-10 | 30-60 secs. | 20 |
| | Hydrogen peroxide | 60 | | |
| | Water | 30 | | |

Obviously, the procedure for titanium should not be used if high specific activity fluorine-18 is desired from this target. In this case, mechanical cleaning is recommended, using only non-fluorine containing abrasives and other materials.

## 6.3 PREPARATION OF SOLID TARGETS BY ELECTRO-DEPOSITION

Many useful radionuclides can be produced with the available cyclotrons using solid target technology. In order to be reliable, plated targets must meet a series of requirements. In this chapter, Tl-201 is used as an example of the target preparation and processing. Further material on other radionuclides can be found in an IAEA TRS report 432: Standardized High Current Solid Targets for Cyclotron Production of Diagnostic and Therapeutic Radionuclides.

For most solid targets, the best method for producing targets that will withstand high beam currents and yet can be easily processed is electroplating. Good thermal contact between the target material and the cooling plate allows beam currents to be higher; and by using electrochemical processing and recovery of the material, the processing is greatly simplified [8-12].

### 6.3.1 Physio-chemical Requirements on Metal Layers

There are several prerequisites for the successful preparation of a solid target. The requirements for a solid target are as follows:

- The layer must be homogeneous over the entire surface area to ±5%.
- The layer must adhere strongly to the carrier up to the irradiation temperatures.
- The layer must be smooth (not spongy), dense (no occlusions nor vacuoles), and stress free.
- The layer must be free of any organic plating additives (complexing agents or surfactants).

Given these requirements for a good quality target, a 'poor quality' Tl-203 target layer means that one or more of these conditions are not satisfied. The main causes for poor quality layers are:

- Gas (hydrogen) evolution at the cathode during plating resulting in spongy and irregular deposits.
- Concentration polarization of the electro-active species (i.e. the hydrated or complex target metal ion) giving rise to treelike structures called dendrites, requiring post-plating mechanical fashioning such as rolling with enhanced risk of plating solution occlusions.
- Ill-considered choice of additives such as organic complexing agents and tensides bringing about peeling off of the target layer and/or target damage on irradiation.
- Unidirectional stirring and maladjusted plating temperature causing inhomogeneous layers and dendrites.
- Non-homogeneous electrical field and badly adjusted plating voltage wave form causing inhomogeneous layers and dendrites.

There are additional chemical requirements for an industrial process concerning the solutions, setups, and other conditions. These are:

- The plating solution must be free of toxic ions (e.g. $CN^-$).
- It must be well suited for repetitive plating (up to 10 batches) at room temperature.
- It must be possible to prepare several targets at the same time with a minimum of four.
- It should be possible to complete the processing in one shift (7 hrs.).
- The layer thickness should be time controlled (100% plating current efficiency).
- Post plating mechanical preparation such as pressing and rolling must be excluded.

### 6.3.2. Simultaneous Multi-target Preparation

The goal of the plating methodology used here is to produce a homogeneous electric field over the entire cathode surface area, a homogeneous layer thickness, and to plate several targets at the same time to increase consistency and production efficiency. Simultaneous multi-target plating resulting in homogeneous target metal layers requires an appropriate plating vessel design to ensure a homogeneous electric field. It also requires a well-designed stirring system that avoids local concentration gradients and hence local concentration polarization of the electro-active species.

As far as the plating vessel is concerned, a cylindrical geometry is recommended. The requirements can be met by using a hollow Perspex cylinder showing an appropriate diameter/height ratio (typically 1/3) and, for an even number of targets (n = 4,8), a diameter/(n)(w) ratio of 1.25, where w equals the width of the plating area of a single target, and n is the number of targets. The vessel should be fitted with a single axial and grounded Pt anode wire (1mm) mounted in the bottom, and properly shielded at both ends. Four (or eight) vertical slots in the outside wall of the cylinder allow the introduction of four target carriers. The geometry results in a quasi-homogeneous electrical field at the surface of the cathodes.

The stirring system should allow fast and efficient homogenization of the plating solution. This is feasible by introducing a hollow, perforated Perspex, or POM cylinder surrounding the Pt anode and mounted on the axis of a DC motor-tacho combination with variable rotation speed (up to 1200 rpm), while the direction of rotation should be reversed periodically (typically every 8 seconds). The vigorous bi-directional stirring reduces the thickness of the hydrodynamic layer and hence the concentration polarization. The geometry of the stirrer (length of the cylinder and number and diameter of the circular holes) needs some optimization for narrow ($d < 4.5$ cm) plating vessels.

The plating temperature is an important quality parameter for some noble metals such as rhodium. At higher temperature the viscosity of the solution decreases and the mobility of the ions increase while in well-stirred conditions, the thickness of the hydrodynamic layer is substantially reduced. Higher temperature, therefore, reduces concentration polarization. On the other hand, over-voltages are lowered at higher temperatures, even for heavy metals such as thallium, with an increased risk for hydrogen gas evolution. Furthermore, the required electromechanical plating set up should be much more sophisticated (heating element and associated feedback electronics for temperature control, solution level monitoring and feedback electronics to add water to compensate for evaporation).

The optimum temperature for a given metal electrolysis can only be determined experimentally. Whenever possible, plating at room temperature is preferred. An example of a multi-target plating apparatus is shown in Figure 1.

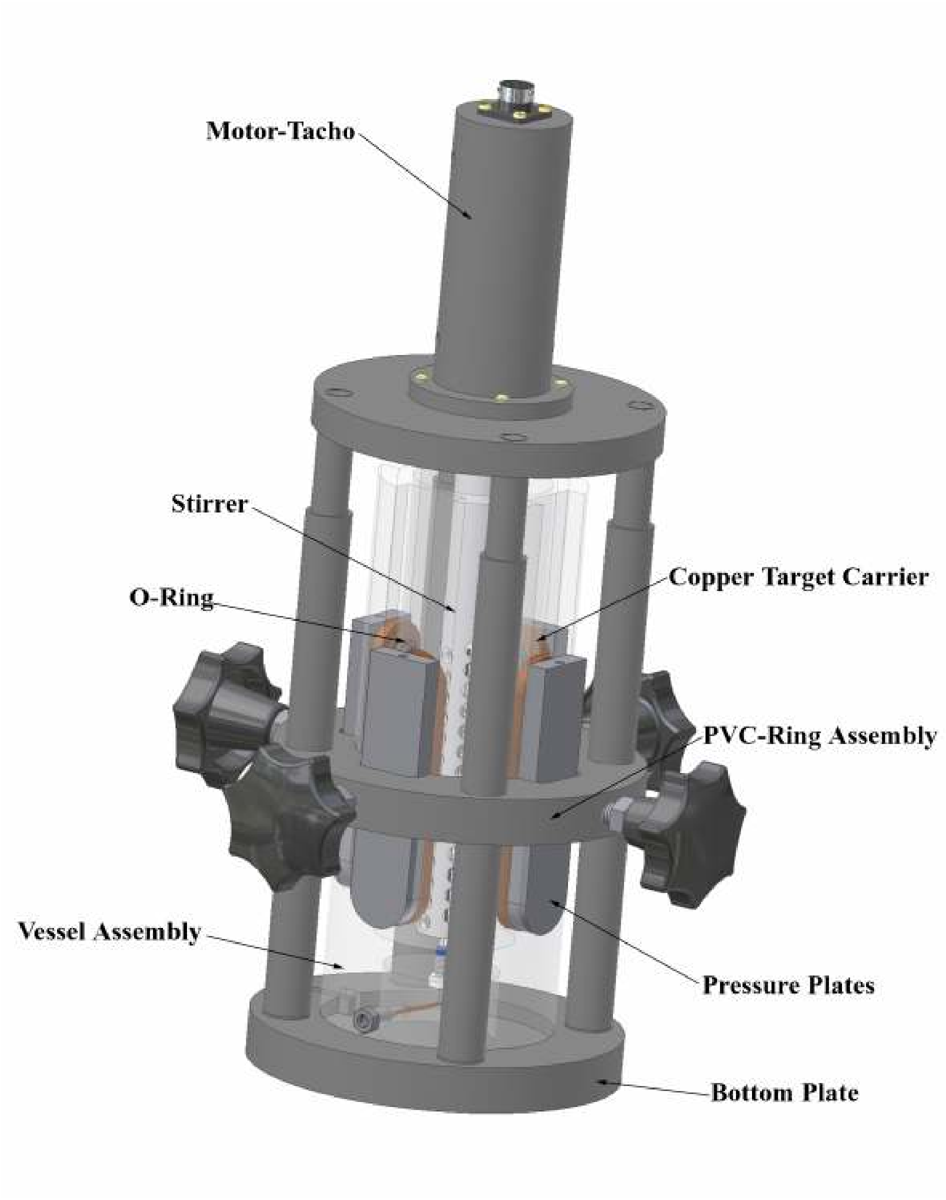

*FIG. 1. Diagram of the four target plating chamber*

A picture of the four target chamber is shown in Figure 2 showing the Perspex cylinder, the perforated stirrer and the slots where the target plates can be mounted.

*FIG. 2. Plating apparatus for plating four targets simultaneously. The materials of construction are Lucite for the bath and other plastics for the other elements*

An eight target set up is shown in Figure 3. The electro-deposition vessel is fitted with an axial Pt wire anode mounted in the bottom by means of a tube-end fitting with perforated septum. Eight vertical slots in the outside wall allow introduction and positioning of eight Cu target carriers.

*FIG. 3. Bath for production of eight targets simultaneously*

The target carriers are copper backing plates onto which the target material is deposited. The plates are water cooled to prevent damage or volatilization of the target material during irradiation. Typical target plates are shown in Figure 4.

*FIG. 4. On the left is the front view of the target carriers and on the right is the side view showing the water cooling connections*

The schematic diagram of a plating electronics is represented in Figure 5. Note the Figure 5 shows the electronics setup for a four plate bath.

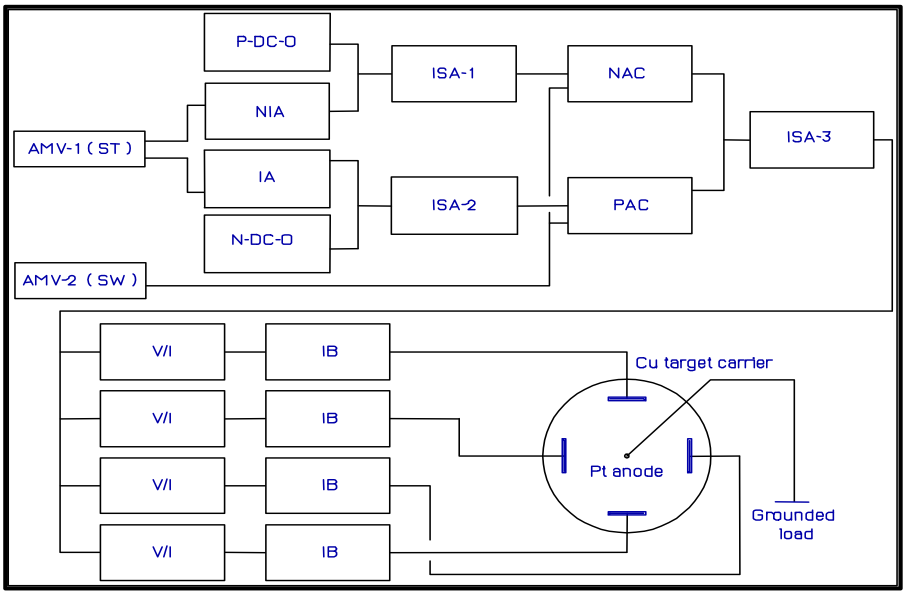

*FIG. 5. Electronics diagram of the plating bath*

An astable multivibrator (AMV-1) generates a saw-tooth (ST) signal of appropriate frequency and duty cycle. The ST signal is amplified by a non inverting amplifier (NIA) and summed with a positive DC offset voltage (P-DC-O) by an inverting summing amplifier (ISA-1). The output forms the base for the positive alternation of the compound signal. The ST signal is amplified by an inverting amplifier (IA) and summed with a negative DC offset voltage (N-DC-O) by an inverting sum amplifier (ISA-2). This output forms the base for the negative alternation of the compound signal. An astable multivibrator (AMV-2) generates a square wave (SW), with appropriate frequency and duty cycle, which chops the output of ISA-1 and ISA-2 in such a way that only one alternation is active at the same time.

The outputs of the negative alternation chopper (NAC) and the positive alternation chopper (PAC) are summed in an inverting amplifier (ISA-3) which output delivers the compound signal. This signal is fed into four independent voltage-to-current (V/I) converters with associated push-pull current boosters (IB) and grounded load. This circuitry allows the simultaneous deposition of four Tl targets at four different current densities using a single and grounded Pt-anode.

The electro-deposition electronics consists of a rack with

8 Eurocards
2 power supplies
1 tirrer controller
1 signal generator
8 voltage-to-current (V/I) converters with associated push-pull current boosters

A picture of the complete electronics is shown in Figure 6.

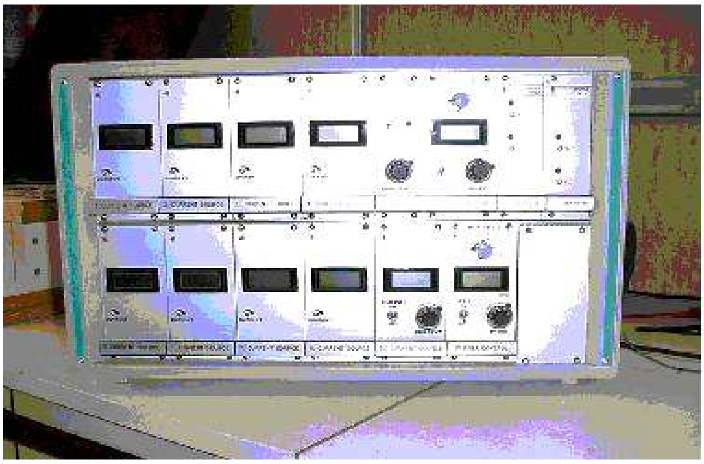

*FIG. 6. Eight Target Electronics*

### 6.3.3. Optimization of Plating Technology

There are four fundamental plating methods which can be used. Each of these has some advantages and disadvantages which are described in the next section.

In constant voltage electrolysis (CVE), a fixed voltage is applied between the anode and the target carrier cathode immersed in the plating bath. During electrolysis, the current is decreasing as a result of depletion of the electro-active species (hydrated or complex metal ions), and the cathode potential shifts towards more negative values. This carries with it an enhanced risk for hydrogen evolution. This can be prevented by the addition of a suitable cathodic depolarizer ($NO_3^-$) that fixes the cathode potential at a constant value and that is reduced to a non volatile species ($NH_4^+$) in acid medium. Though this technique is frequently used in industrial coating and in analytical electro-gravimetry, the current efficiency (and hence the plating current density) varies during the plating process and is generally much less than 100%, making the method less attractive for time-controlled layer thickness plating.

In constant current electrolysis (CCE) a fixed current is forced through the electrochemical cell and the applied plating voltage automatically adjusted (i.e. increased) such that the set current is kept up. Using concentrated solutions of appropriate composition that show a limited depletion ratio for the electro-active species (maximum 50 %) at the end of the plating and applying an optimized plating current density, a 100% current efficiency can be easily obtained.

For time-controlled layer thickness plating, Controlled cathode potential electrolysis (CCPE) technique is preferred. CCPE involves the introduction of a reference electrode into the system. The potential of the cathode is set at a fixed value versus the potential of the reference electrode. This value corresponds to 99.99% depletion of the electro-active species, i.e. to the lower limit of its discharge interval. The current decreases exponentially as the process progresses and its reading may be used to monitor the depletion of the bath. CCPE is well-suited for quantitative separation of metals and is a very attractive tool in the frame of the recovery of enriched target material.

Internal electrolysis (IE) does not involve the application of an external voltage or current source to the electrochemical cell built up from two different electrodes. External short-circuiting of both electrodes results in a spontaneous current that decreases exponentially as a function of time. The anode dissolves and the electro-active species wanted is quantitatively plated out onto the cathode. This method has a limited number of applications and was frequently used in destructive neutron activation analysis in the sixties. It is not suited for thick target preparations. Given these characteristics, CCE should be preferred for the preparation of high current beam cyclotron targets, and CCPE should be used for purification and recovery of enriched material.

In spite of the optimized conditions discussed above, a slight tendency towards dendrite formation is found when DC constant current electroplating is performed. This phenomenon can be suppressed completely by application of AC voltages and currents. During the cathodic part of the applied signal deposition, micro dendrite formation takes place, but during the anodic part the metal is redissolved. This redissolution rate is higher for fine treelike structures (showing a high surface area per unit of mass) than for real massive crystals. Appropriate choice of the wave form of the AC signal and of the amplitudes of the cathodic (ic) and anodic (ia) currents (ic > ia) results in a net cathodic deposition with suppressed dendrite formation. Of four different wave forms tried, a bipolar chopped saw-tooth gives the optimum results in the case of thallium. The signal frequency equals 100Hz, the chopper frequency is 1000Hz, and the chopper duty cycle amounts to 60%. The wave form is schematically represented in Figure 7.

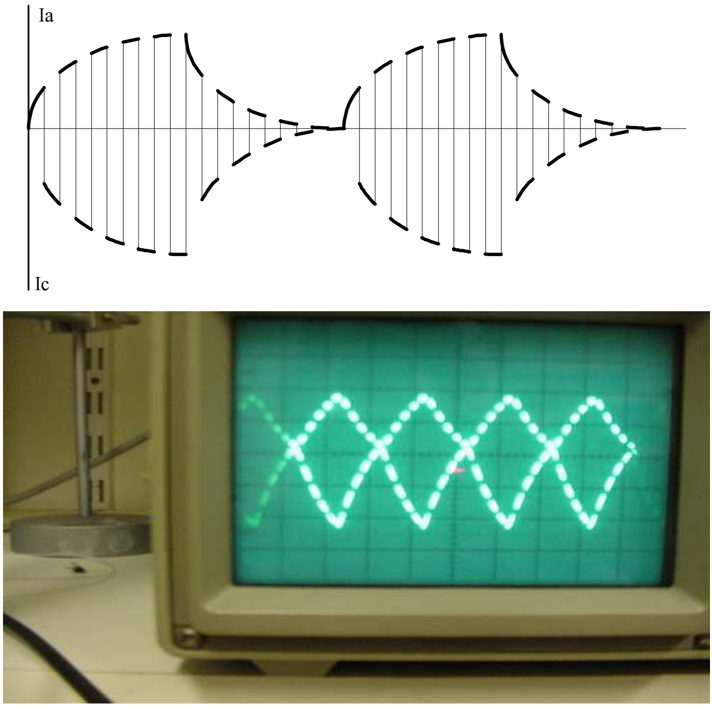

*FIG. 7. Bipolar chopped saw-tooth plating voltage upper diagram showing the ideal situation, and the lower diagram showing the oscilloscope trace of the voltages applied for the plating of Tl-203*

## 6.4 EXAMPLE OF THALLIUM-201 PRODUCTION

Thallium-201 has been chosen as an example of typical production conditions and procedures. Similar procedures may be used for other target materials.

### 6.4.1 Cleaning of Target Carriers (Cu backings)

The following steps should be carried out to clean the surface prior to electro-deposition:

- Rub the deposition area of the Cu backing successively with abrasive wool type 1 and type 2 for 1 minute, respectively;
- Rinse with water;
- Rinse with acetone;
- Dry the carrier with adsorbing paper and weigh the carriers;
- Introduce the backings in the four slots of the deposition vessel and turn the knobs of the mechanical pestles in pairs, clockwise to ensure liquid tightness.

### 6.4.2 Electroplating Bath

A thallium metal layer, which meets all metal layer quality requirements and all industrial demands, can be obtained by CCE of Tl-203 from alkaline (pH>12), solutions which contain concentrated monovalent Tl (holding an amount of Tl that is equal to twice the amount plated out), 0.5 M in EDTA, a non-incorporated surfactant (BRIJ-35), and a strong reducing anodic depolarizer (hydrazine hydrate). By applying a bipolar chopped saw-tooth (fST= 100Hz; fCH= 1000 Hz; CDC=60%) to the cylindrical plating vessel as described in the previous section, the following results are obtained:

Relatively high maximum allowable current density (2 to 3 mA.cm$^{-2}$) allowing simultaneous time-controlled (plating current efficiency = 100%) production of 4 targets carrying more than 100 mg Tl-203 per square centimeter within less than 6 hours and requiring no post-plating mechanical fashioning;

Plating performed from cyanide free solutions that are well-suited for repetitive plating cycles (up to 10 batches) by simple adjustment of the metal contents of the plating bath and from which the remaining enriched material can be readily recovered by controlled cathode potential electrolysis;

Target layers that are homogeneous (±5%), smooth (dendrite free), dense (no occlusions, nor vacuoles) and free of traces of organic bath additives (EDTA, BRIJ-35). The layer remains intact and strongly sticks to the copper target carrier up to 270°C, a temperature about 30°C below the melting point of the metal.

Specific procedures for these plating techniques can be found in the IAEA TRS Report 432: Standardized High Current Solid Targets for Cyclotron Production of Diagnostic and Therapeutic Radionuclides.

Tl-203 layers (surface area 11.6 cm$^2$, total amount of thallium, 1.1gram) plated on IBA copper carriers in this way can withstand a 9 hour irradiation with a circularly wobbled 270 µA proton beam without loss of material.

Figure 8 is a picture of typical Tl-203 target after plating procedure.

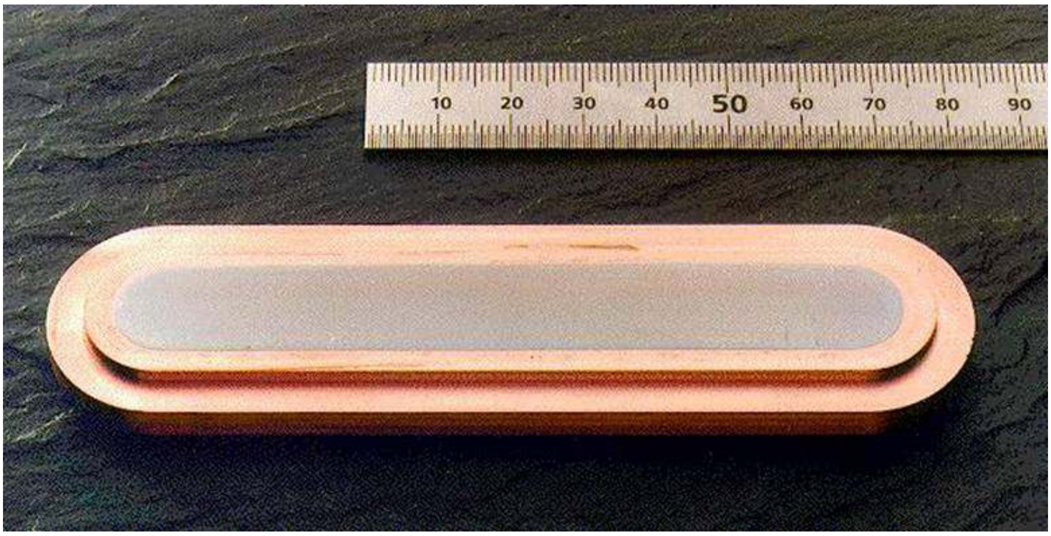

*FIG. 8. Tl-203 plated on copper target plate*

## 6.5 PLATING SOFTWARE EXCEL PLATING WORKBOOK

An Excel workbook is contained in the CD accompanying this book which can calculate the conditions for electroplating (Appendix 3).

## 6.6 THALLIUM TARGET QUALITY CONTROL

There are two important aspects of quality control for this procedure. The first is in the plates that are being used for irradiation. These plates must meet certain quality assurance guidelines, or they are likely to be damaged in the beam and produce low yields of Tl-201. The other aspect is the quality control of the final product. These tests are critical for the release of the Tl-201 for use.

### 6.6.1 Quality Control of Tl-203 Plates

The new electroplating technology from alkaline EDTA solutions allows the production of high quality Tl-203 targets that do not require any post-plating mechanical smoothing. The homogeneity of the thallium layer, determined by micrometry (12 measurements spread over the surface area) is acceptable: a standard deviation on the mean thickness of less than 5% is observed. The surface area granulometry (visual microscopic inspection, X250 SEM shots) is excellent as compared with that of targets plated from acid plating baths. The granulometry obtained may be used as a reference for future thallium plating techniques. Because the melting point of thallium metal is low (303.5 °C), the thermal shock test should be performed at 270°C. Heating up to this temperature in the air followed by submersion in cold water (15°C) and multiple bending does not give rise to crater formation nor peeling off. This proves that no plating additives (EDTA, BRIJ) are present in the thallium metal lattice or at the thallium/copper carrier interface. Application of the plating technology in industry resulted in an increase of the $^{201}$Tl yield up to 20%, as compared with that obtained with targets plated from acid solutions.

### 6.6.2 Quality Control of Tl-201 Product

The $^{201}$Tl produced by using the new plating technology meets all chemical, radiochemical and radionuclidic quality criteria required by the pharmacopoeia.

## 6.7 IRRADIATION OF ELECTROPLATED SOLID TARGETS

There are several factors which contribute to the maximum beam currents which may be run with a solid target. The beam density is the primary factor. If there are 'hot' spots in the beam, the highest current at which the target may be run will be much lower than if the beam has a uniform profile. Target cooling is another factor and some examples of calculations for optimizing the cooling based on the geometry of the target and backing plates are given in Section 6.7.1.

### 6.7.1 Heat Transfer Model

The thallium target can be considered as a three-layer system, facing the accelerator vacuum on one side and the coolant fluid on the other (see Figure 9).

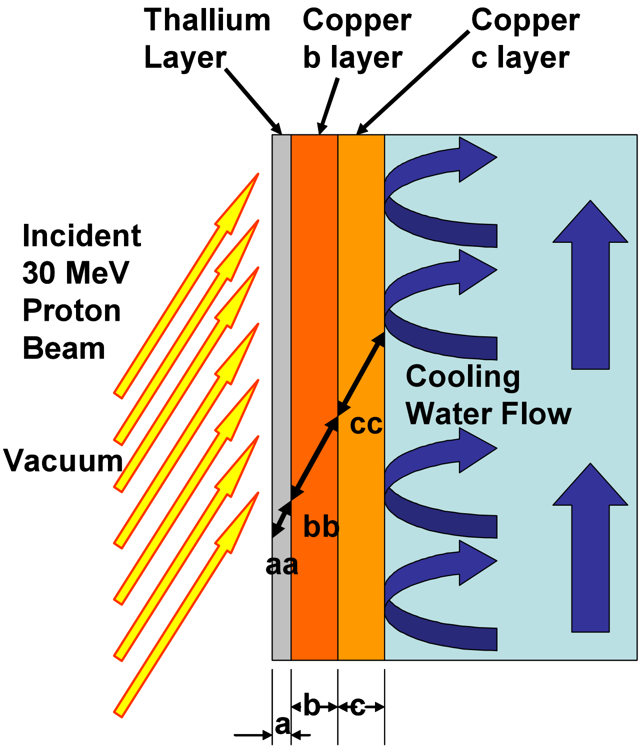

*FIG. 9. The three layers of a thallium target*

Layer 1, the $^{203}$Tl deposit, has a physical thickness of 80x10$^{-4}$ cm, denoted by a in the diagram. In this layer $^{201}$Pb is produced by the $^{203}$Tl(p,3n)$^{201}$Pb threshold reaction provoked by 30 MeV protons impinging under a θ° beam-target angle. Due to excitation, ionization and bremstralung, protons do lose kinetic energy in this layer that is converted into heat. Assuming homogeneous irradiation, that is the current density (µA.mm$^{-2}$) is constant over the whole surface area S (= 11.69 cm$^2$), the total heat production rate $q_{Tl}$ (J.s$^{-1}$), and the heat production rate per unit of volume $q'''_{Tl}$ (J.cm$^{-3}$.s$^{-1}$) in this layer are related as:

$$q_{Tl} = q'''_{Tl} * a * S$$

Layer 2, the Cu-b layer, has a physical thickness of b cm. In this layer protons emerging from the Tl layer are stopped completely. The heat production rate $q_{Cu}$, and the heat production rate per unit of volume $q'''_{Cu}$ in this layer, are linked by:

$$q_{Cu} = q_{Cu}^{'''} * b * S$$

Layer 3, the Cu-c layer, has a physical dimension of c cm and merely serves as mechanical support for the Tl layer. The total heat ($q_T$) produced in the layers $q_{Tl}$ and $q_{Cu}$ is transferred to the coolant fluid through this layer by conduction.

$$q_T = q_{Tl} + q_{Cu}$$

At the Cu-c/coolant interface, the heat is transferred to the coolant by convection solely, that is no sub-cooled nucleate boiling occurs, and the bulk temperature of the coolant is a constant ($T_w$).

In steady state conditions, the heat and heat transfers do result in a temperature profile represented in Figure 10.

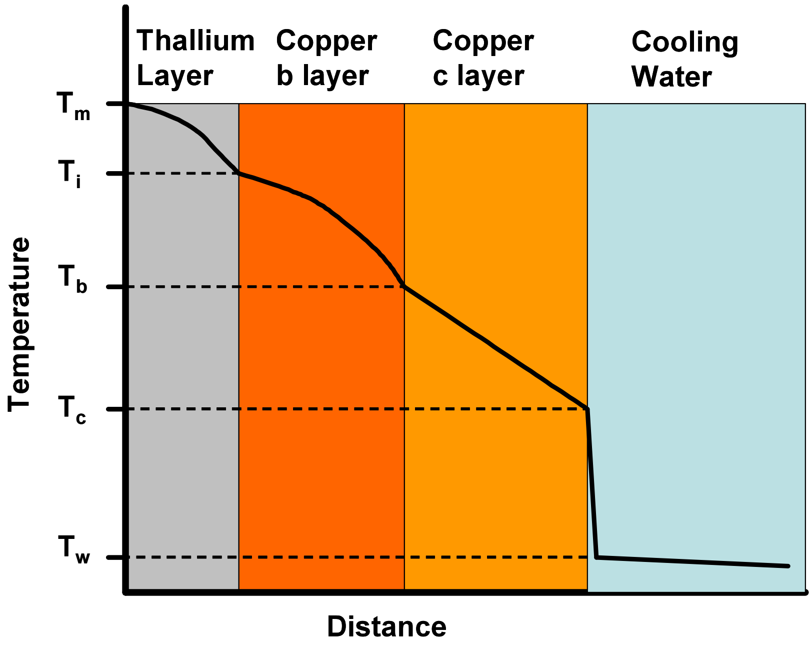

*FIG. 10. Temperature profile through the thallium target*

Where:

$T_m$ is the maximum temperature at the vacuum/Tl interface
$T_i$ is the temperature at the Tl/Cu-b interface
$T_b$ is the temperature at the Cu-b/Cu-c interface
$T_c$ is the temperature at the Cu-c/coolant interface
$T_w$ is the temperature of the coolant

A detailed analysis of the heat transfer and temperature profile of the solid targets is given in Appendix 1.

## 6.8 ACCELERATOR BEAM PROFILES

Beam current density is often a critical parameter in determining how much radionuclide can be produced in a target. If the current density is too high, the solid target may be burned and the fluid target (gas or liquid) may have very large density reduction.

If the beam has 'hot spots' (spikes in the beam intensity), there may be areas where the solid target material is burned away or in the case of fluids, areas where the target material is pushed aside. All the above conditions will result in a loss of yield and, therefore, the beam current density should be as uniform as possible. Negative ion machines have an advantage over positive ion machines in this respect. Since the negative ion machine uses a foil to extract the beam, this tends to make the beam more homogeneous. It is possible to calculate this effect by using the equations for small angle multiple scattering found in Chapter 5 (Section 5.3.4) or with the SRIM Monte Carlo simulations (www.srim.org).

If we assume a Gaussian current density distribution at the exit of a cylindrical collimator as described by the following equation:

$$i = i_m . e^{-a^2 r^2}$$

with $i_m$ is the maximum current density (μA.mm$^{-2}$)
$a^2$ is the Gaussian exponent = $1/2\sigma^2$ (mm$^{-2}$)
σ is the standard deviation of the Gaussian distribution
r is the radial distance from collimator circle

The total beam current $I_B$ is given by:

$$I_B = \int_0^\infty i_m . e^{-a^2 . r^2} 2\pi r dr = -\frac{\pi * i_m}{a^2} . \int_0^\infty d(e^{-a^2 . r^2}) = \frac{\pi * i_m}{a^2}$$

and the target current, $I_T$, is given by the equation:

$$I_T = \int_0^R i_m . e^{-a^2 . r^2} 2\pi r dr = -\frac{\pi * i_m}{a^2} . \int_0^R d(e^{-a^2 . r^2})$$

$$I_T = \frac{\pi * i_m}{a^2} (1 - e^{-a^2 . R^2})$$

The beam current efficiency $\varepsilon_B$ can be defined as:

$$\varepsilon_B = \frac{I_T}{I_B} = (1 - e^{-a^2 . R^2}) * 100$$

Which is the percentage of the total beam current striking the target.

In Table 3, the beam current efficiency is represented as a function of the FWHM and sigma.

TABLE 3. BEAM CURRENT EFFICIENCY $\varepsilon_B$ FOR DIFFERENT BEAM SHAPES PASSING THROUGH A 20 CM COLLIMATOR

| FWHM (mm) | Sigma (mm) | $\varepsilon_B$ | % lost on Collimator |
|---|---|---|---|
| 5 | 2.1 | 100 | 0 |
| 10 | 4.3 | 98 | 2 |
| 15 | 6.4 | 88 | 12 |
| 20 | 8.5 | 76 | 24 |

The following Figure 11 graphically demonstrates the beam profiles for the beams of different FWHM. One can also see the amount of beam lost on the 20 cm diameter collimator. The total beam current on the target is the same for all the distributions.

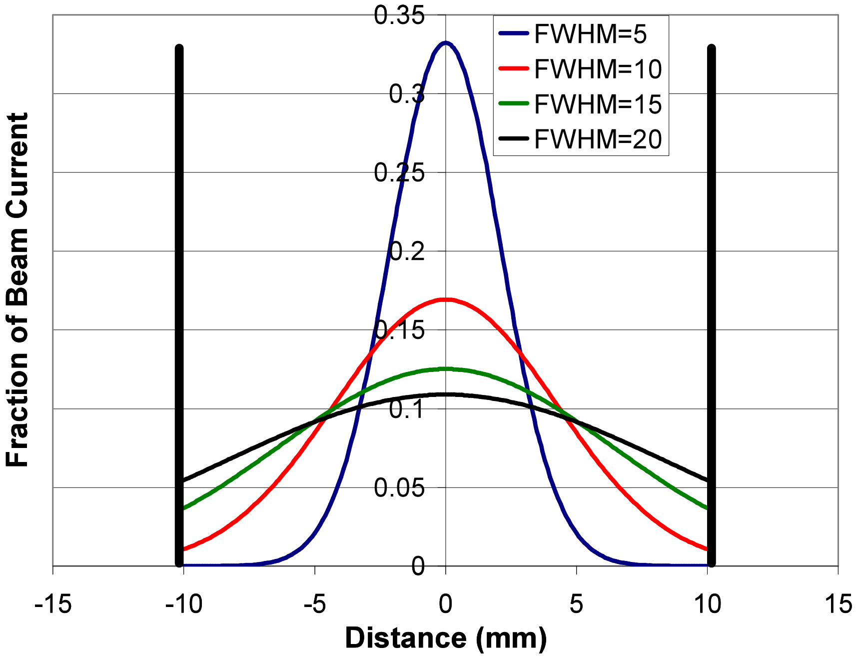

*FIG. 11. Beam profile of beams passing through a 20 cm diameter collimator with differing Gaussian distributions*

It can be seen from this graph that the current density is much higher for the narrower beam than it is for the beam with the wider distribution. Since the amount of beam which may be put on a target is a function of the current density, the more uniform distribution is usually the preferred distribution. In the above case, for the narrowest distribution, about 77% of the beam will be in the central 5.0 mm diameter spot; whereas only about 31% of the widest beam will be in this same area. If we assume a 50 microamp beam current and a 15 MeV beam energy, the target will have a power density of nearly 3000 watts/cm$^2$ with the narrow beam and a power density about 1200 watts/cm$^2$ with the widest distribution. For a detailed calculation of what effect this will have on the heat transfer and the maximum current that may be put on a solid target, see Appendix 1 in the CD attached to this publication.

### 6.8.1 Beam Wobbling During Irradiation

One of the best ways to decrease the current density on a particular target is to wobble the beam over the entire surface of the target. This smoothes out beam irregularities ('hot spots') and allows the target to be run at higher beam currents. Further increases of the beam current can be obtained by circular wobbling. Therefore, the Gaussian distribution is shifted over a distance RW, the wobbling circle radius, from the collimator axis where after the proton beam is forced to rotate around the axis as shown in Figure 12.

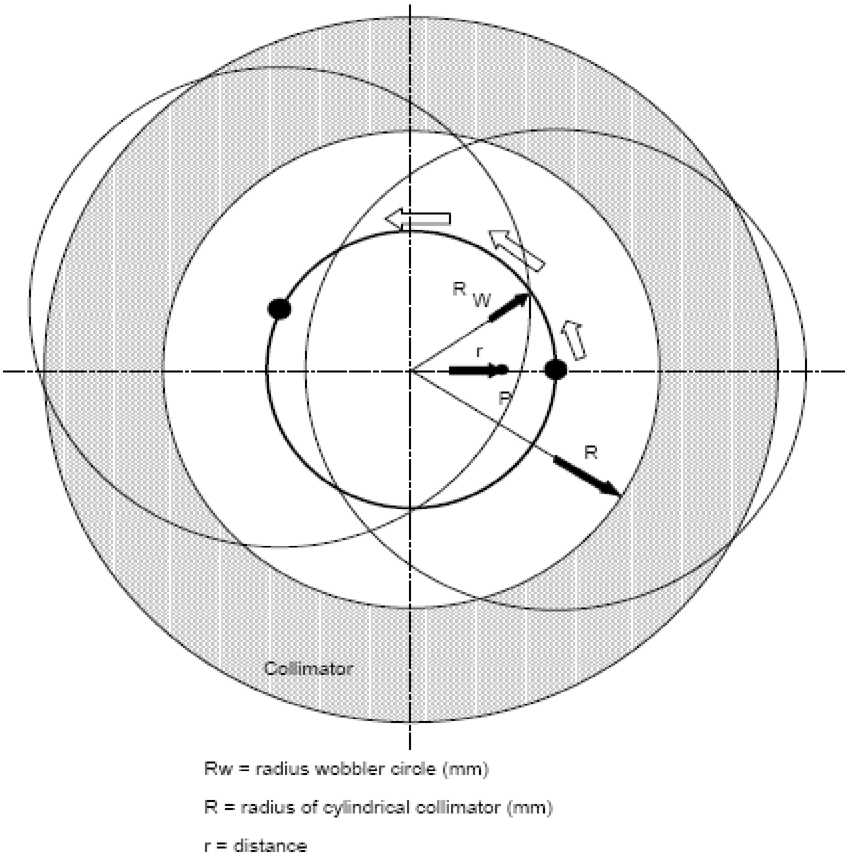

*FIG. 12. Circular Wobbling of the Beam during Irradiation*

Though a part of the beam is collected on the collimator body, further increase of the target current can be expected by optimizing the radius of the wobbling circle. The calculations of the mean current density distribution and of the total beam and target current cannot be done analytically: numeric integration is required. An example of a typical beam current distribution in two dimensions is shown in Figure 13.

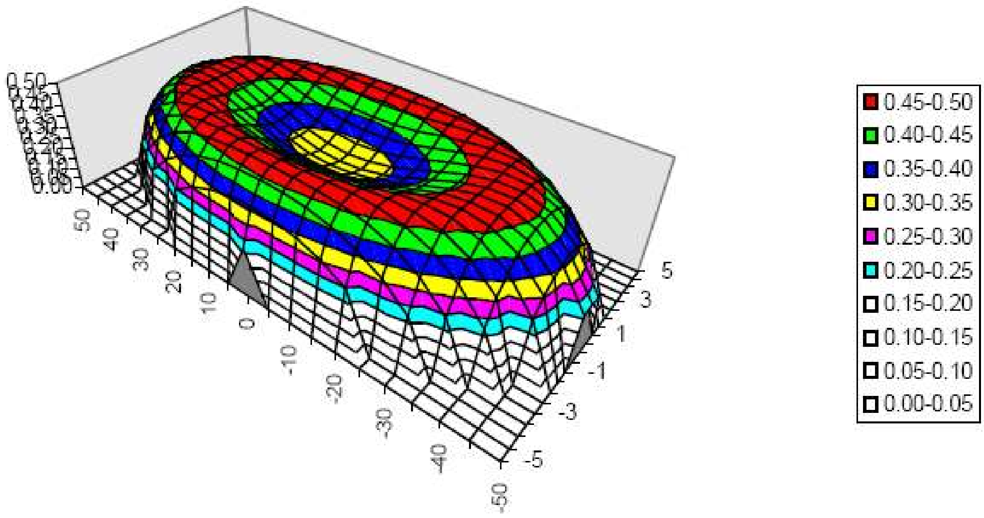

*FIG. 13. Current density distribution for a wobbled beam*

This density distribution can then be applied to the heat transfer model to determine the temperature profile across the target. This will in turn give an indication of the maximum beam current which may be applied to the target without incurring any damage. A caveat here is to note that sparks in the cyclotron vacuum tank may cause severe distortions in the beam shape and, therefore, give rise to transient spikes in the beam current distribution. For this reason, a common practice is to limit the beam current to 50% of that calculated as the maximum allowable beam current using these approximations.

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# 7 TARGET PROCESSING

## 7.1 INTRODUCTION

The processing of the target after irradiation is one of the most critical steps in the production of radioisotopes. Each of the three states of matter poses specific problems in the recovery of the radioisotope. In the case of gases, the transfer out of the target is relatively simple; using pressure gradients or sweep gases, but the lines must be kept free from leaks in order to maintain the purity of the gases and to prevent any contamination of the surrounding area. The radioisotope must be trapped or separated from the target gas or in the case of some gaseous targets where the radioisotope is deposited on the walls of the target during irradiation; it must then be brought into solution and removed.

In the case of liquid targets, it is often possible to transfer the liquids over short distances using push gases, although there may be a problem in transferring all of the material since droplets may stick to the walls of the transfer line. A special problem with liquid targets is the tendency of the liquid to dissolve some material from either the vacuum isolation foil or from the target body. These impurities may be radioactive, or they may be a metal salt, or colloid. In all cases, they must be removed from the liquid before synthesis.

In the case of solid targets, the problem is usually to remove the radioisotope from the target matrix efficiently. The techniques used may be thermal diffusion, dissolution with solvent extraction, separation with ion exchange resins, or electrochemical separation. There are some examples of some of these techniques included in this chapter, but the particular conditions and reagents will need to be gathered from the literature.

Another important aspect of target processing is the recovery of enriched isotopes used to make the target. This can have substantial economic implications since the enriched isotopes can be very expensive and few centers can afford to waste these isotopes. For liquids and gases, this often means a simple extraction using resins or a cryogenic recovery of the target gas. In the case of solid targets, a more elaborate electrochemical recovery may be required.

## 7.2 SPECIFIC ACTIVITY

Specific activity is the number of radiolabeled molecules compared to the total number of molecules and is usually expressed as a unit of radioactivity per mole of compound. It is further defined in Chapter 2. Specific activity is a critically important property in the preparation of radiotracers. It is particularly important in PET, where the radionuclide is incorporated into a radiotracer that is used to probe some physiological process, in which very small amounts of the native biomolecule are used. When carrying out these studies, such as probing the number of receptors or the concentration of an enzyme, considerations of the total mass of compound injected become even more important [1, 2]. There is, of course, an ultimate limit to specific activity when only the radioactive atoms or radiolabeled molecules are present. The characteristics of some radioisotopes are shown in Table 1.

As an example, the typical specific activities for $^{11}C$ labeled molecules are in the order of 10 Curies/µmole (370 GBq/µmole). Hence, it can be seen that only 1 in 1,000 tracer molecules is actually labeled with carbon-11. The rest contain carbon-12. There is a clear need to reach reliable production of high specific activity radiopharmaceuticals.

Present-day tracers and certainly future tracers include receptor/transporter-ligands that are very potent and, therefore, require very little mass to activate the receptor. In order for PET to be a true tracer technique, receptor occupancy with the radiolabeled tracer should be kept below 5% in order to avoid pharmacological or pharmacodynamic effects.

TABLE 1. DECAY CHARACTERISTICS AND MAXIMUM SPECIFIC ACTIVITY OF SOME IMPORTANT RADIONUCLIDES

| Nuclide | Half-life (min) | Decay Mode | Max. Specific Activity (theo.) |
|---|---|---|---|
| C-11 | 20.4 | 100% $\beta^+$ | 9220 Ci/µmole (341 TBq/µmole) |
| N-13 | 9.98 | 100% $\beta^+$ | 18900 Ci/µmole (700 TBq/µmole) |
| O-15 | 2.03 | 100% $\beta^+$ | 91730 Ci/µmole (3394 TBq/µmole) |
| F-18 | 109.8 | 97% $\beta^+$ | 1710 Ci/µmole (63.4 TBq/µmole) |
| Cu-62 | 9.74 | 99.7% $\beta^+$ | 19310 Ci/µmole (714 TBq/µmole) |
| Ga-67 | 4696.8 | 100% ε | 40 Ci/µmole (1.5 TBq/µmole) |
| Ga-68 | 68.0 | 89% $\beta^+$ | 2766 Ci/µmole (102 TBq/µmole) |
| Br-75 | 96.0 | 75.5% $\beta^+$ | 1960 Ci/µmole (73 TBq/µmole) |
| Rb-82 | 1.25 | 95.5% $\beta^+$ | 150400 Ci/µmole (5565 TBq/µmole) |
| In-111 | 4048.8 | 100% ε | 46 Ci/µmole (1.7 TBq/µmole) |
| I-122 | 3.62 | 75.8% $\beta^+$ | 51950 Ci/µmole (1922 TBq/µmole) |
| I-123 | 793.4 | 100% ε | 237 Ci/µmole (8.8 TBq/µmole) |
| I-124 | 6019.2 | 23.3% $\beta^+$ | 31 Ci/µmole (1.15 TBq/µmole) |
| Tl-201 | 4374.7 | 100% ε | 42.6 Ci/µmole (1.58 TBq/µmole) |

## 7.3 GAS TARGET PROCESSING

When a gaseous target is irradiated, it is very often done with a high pressure of gas in the target. Pressures can be anywhere from 2 atmospheres to 50 atmospheres. The gas may be retained in the target during bombardment; or it may be processed in a flow mode, where the target gas flows through the target during irradiation.

### 7.3.1 Gaseous Transfer

In a flow through target, a gas flow is established based on the pressure in the target during bombardment. This pressure is usually set with a regulator and is at equilibrium. In a closed target, when a valve is opened which connects the target to a processing module or other trapping station, the gas will flow along the pressure gradient to the desired location. If the pressure is low or the volume of the line is high, then a push stream of gas is often used to increase the efficiency of the transfer. In either case, the flow rate through the tubing is usually given by the Poiseuille equation. This equation holds if the flow is laminar.

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

Where:
F is the flow in $cm^3$/sec
g is the gravitational acceleration (980.6 $cm/sec^2$)
r is the radius of the tubing (cm)
L is the length of the tubing (cm)
µ is the viscosity in poise (g/cm-sec)
ΔP is the pressure differential ($g/cm^2$)

The Reynolds number can be calculated to determine if the flow is really laminar or not. This relation is:

$$Re = \rho . V. D / \mu$$

Where:

Re is the Reynolds number (dimensionless)

V is the flow velocity (cm/sec)

$\rho$ is the density (g/cm$^3$)

$\mu$ is the viscosity in poise (g/cm-sec)

D is the tube diameter (cm)

If the Reynolds number is greater than about 2000, then the Poiseuille equation is not valid and the flow will be slower than calculated. However, laminar flow is usual for low viscosity gas flows through long, small diameter lines connecting the target to the chemistry lab. Some useful parameters for common fluids at 25°C are given in Table 2. These can be used in the flow equations to get approximate flow rates for gases or for water.

TABLE 2. PARAMETERS FOR COMMON FLUIDS USED TO TRANSFER RADIOACTIVITY

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

Bends or fittings in the line will also slow the flow of the gas. There are tables which give corrections for these which can be found in most mass transfer texts.

Another analysis was carried out to determine the optimum parameters to be used to transfer a gas through a tube at a specified flow rate without the use of metering valves [3] in a constant flow target. A schematic diagram of the situation is shown in Figure 1.

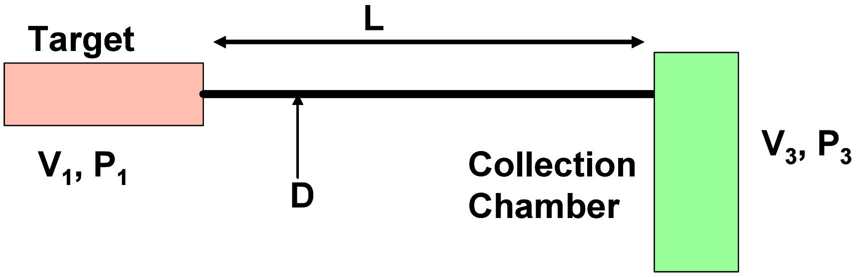

*FIG. 1. Schematic diagram of "tuned" gas transport line*

In this analysis, the equations are:

$$A = \frac{R}{1+\frac{t_1}{\tau}} e^{-\frac{t_2}{\tau}} (1 - e^{\frac{-t_3}{\tau}})$$

When:

$$t_1 = \frac{V_1 P_1}{Q}$$ Target Chamber Dwell Time

$$t_2 = \frac{Ldz}{v(z)}$$ Transit time in tube

$$t_3 = \frac{V_3 P_3}{Q}$$ Collection Chamber Dwell time

Where:

A is the optimum activity delivery rate
$t_1$ is the target chamber dwell time
$t_2$ is the tube transit time
$t_3$ is the collection chamber dwell time
L is the length of the tubing
D is the diameter of the tubing
Q is the mass flow rate
V1 is the target volume
P1 is the target pressure
V3 is the collection chamber volume
P3 is the collection chamber pressure
$\tau$ is the decay constant for the radionuclide ($\ln(2)/T_{1/2}$)
R is the radioactivity production rate

In these calculations, the goals are to:

- Minimize $t_1$ by reducing $V_1$ as much as possible.
- Attempt to match $t_2 = t_3$ to $\tau$.
- Minimize L.
- Use a trap at the outlet to increase the effective $V_3$.

### 7.3.2 In-line Separation and Processing

Whether gaseous radioisotopes are produced in a static target or a continuous flow target, they must be processed before they are ready to be used directly or to be used as a precursor in a more complex chemical reaction. The processing may include trapping the desired radioisotope, converting it to some other chemical form or removing other gaseous impurities in an on-line process. One of the most widely used and simplest processing schemes is for the production of $C^{15}O_2$ from oxygen-15. This on-line processing system is shown in Figure 2 [4]. The oxygen from the target is converted into a mixture of carbon monoxide and carbon dioxide over a charcoal furnace at 525°C. The conversion from CO to $CO_2$ is completed in a cupric oxide furnace at 500°C, and any residual oxygen or ozone is scrubbed out by the elemental copper furnace operating at 300°C.

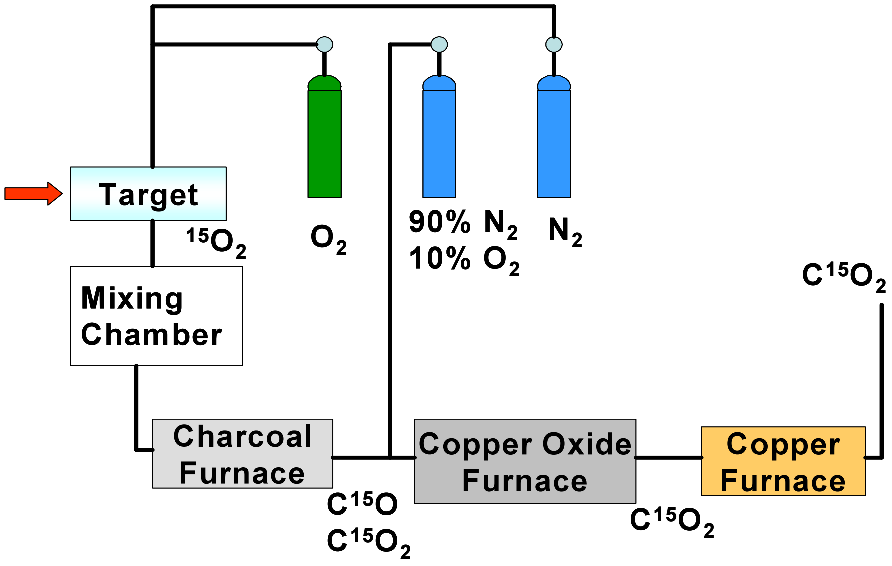

FIG. 2. *Processing system for the production of [$^{15}O$]$CO_2$*

### *7.3.2.1. Trapping of Gases*

One of the most common in-line traps being used is the NOx trap described by Tewson [5]. This trap is used to scrub oxides of nitrogen from the carbon dioxide coming out of the gas target. The oxides of nitrogen are known to interfere with some reactions. They can also be converted to ammonia under some of the same conditions which convert carbon dioxide to methane. Another common in-line trap is a $CO_2$ scrubber used on the inlet to the carbon-11 production target. The removal of carbon dioxide from the nitrogen target gas prior to irradiation helps to increase specific activity. An example for gas processing for $^{81m}$Kr is shown in Figure 3.

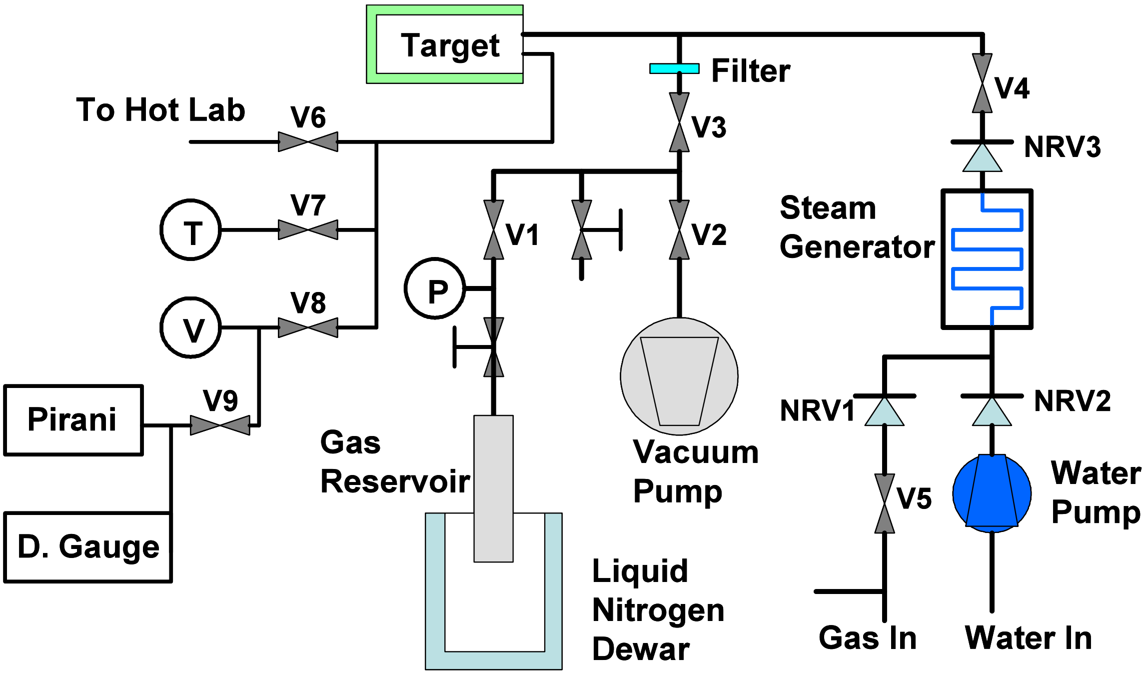

FIG. 3. *Example of a gas handling system for production of Kr-81m. V and P are the mechanical pressure gauges, NRV are one way check valves to prevent backflow*

This system was chosen as an example since it uses almost all of the processes common for gas targets. The system to recycle the target gas, steam the target, and transport the solution to a hot cell for loading onto the generator columns, is illustrated in Figure 3 [6]. All the critical areas use stainless steel piping and 'Swagelok' fittings. A sequence of the steps used in operating this target is given as an example of the steps which usually have to be taken to prepare, use, and clean the gas target. The operating sequence is as follows:

#### *7.3.2.2. System Checks*

- Krypton pressure in gas reservoir
- Sufficient water for steaming
- Sufficient pressure in gas cylinder for target emptying
- Cryogenic Dewar is filled with liquid nitrogen
- All valves closed

#### *7.3.2.3. Target Load Sequence*

i. The target is pumped down by turning on the rotary pump and opening valves V2 and V3. After a delay, V8 opens to allow measurement of the pressure in the target.

ii. To allow a more sensitive measurement of the pressure, valve V9 opens after the mechanical gauge has been below low detection (-25 inches Hg) for 2 seconds.

iii. After the indicated pressure on the Pirani gauge is less than $2x10^{-1}$ mbar, valves V9 and V2 are closed to isolate the target from the vacuum pump and the low pressure sensors.

iv. Valve V1 is opened and then closed once pressure as read on the mechanical gauge has reached 70 psig.

v. Valve V3 is closed to isolate the target and a ready signal is sent to the cyclotron control system; V8 remains open to measure pressure during irradiation.

#### *7.3.2.4. Target Unload Sequence*

i. The heaters for steam generator and target body are turned on to increase the temperature of the target walls.

ii. The cryogenic Dewar is raised slowly to cool the 'pump' gas reservoir.

iii. The cooling of the reservoir is indicated by reservoir pressure falling to 0 psig. After a short delay valves V1 and V3 open to pump out any residual gas from the target.

iv. Valve V9 opens after mechanical gauge has been below low detection for 2 seconds.

v. Wait for absolute pressure diaphragm gauge to reach 19 mbar. This indicates that the target gas has been recovered in the reservoir.

vi. After a delay, ALL valves close and 'blowout' signal sent to target cooling. This closes off the target gas reservoir and sends a gas stream and clears the water from the target cooling lines.

vii. Valves V4 and V5 are opened for short time to relieve target vacuum.

viii. Wait for the steam generator to reach temperature and for the 'blowout' to be completed.

ix. Valve V6 to the hot lab is opened and V4 to the steam generator is opened and a ready signal is sent to the hot cell that radioactivity delivery is imminent.

x. Start water pump to inject steam into the target for a preset time. Steam is used to remove the radionuclide.

xi. The water pump is stopped and valve V5 is opened to empty target to cell, using helium at 50 psig. The helium gas pushes the water through the lines and into the hot cell.

xii. After 9 minutes, close all valves and stop steam generator heater.

xiii. Valves V2 and V3 are opened and rotary pump and target heater runs for one hour. This dries the target and prepares for the next irradiation.

xiv. Heat is turned off and the target remains under active vacuum until next load cycle.

### 7.3.3 Quality Control of Target Gases

The purity of gases used as target gases can have a profound effect on the chemical form of the radioisotope, and on the specific activity of the radioisotope. The specific activity is especially important for carbon-11 containing compounds.

For these reasons, the gases used should be of the highest purity possible and should have a certificate of analysis. This is an extra charge, but is well worth the expense in maintaining the production of the highest quality radioisotopes.

### 7.3.4 Maintenance Schedule for Gas Targets

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 aluminum and Havar, and they have very different characteristics. Aluminum foils often go 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 week end on the first work day.

TABLE 3. SUGGESTED MAINTENANCE SCHEDULE FOR GAS TARGETS

| | |
|---|---|
| Weekly | Visually check for damaged tubing or fittings<br>Leak check the system<br>Check front foil for signs of damage |
| Monthly | Test plastics for radiation damage<br>Track target yields to establish trends |

## 7.4 LIQUID TARGET PROCESSING

There are only a few liquid targets in routine use for radionuclide production. By far the most common liquid target is the oxygen-18 water target for the production of $^{18}F$ using the $^{18}O(p,n)^{18}F$ nuclear reaction. In the water target, the activity is removed in the aqueous phase. There are two general methods of utilization after that. The first is to use the $^{18}O$ water containing [$^{18}F$] fluoride ion directly in the synthesis. This method is used by several people who have small-volume water targets, and the cost of losing the $^{18}O$ water is minor compared to the cost of the cyclotron run. The second method is to separate the fluoride from the $^{18}O$ water, either by distillation or by using a resin column [7-9]. When the resin is used, it can also remove the metal ion impurities from the enriched fluoride solution which, in general, increases the reactivity of the fluoride. The fluoride is usually made more reactive by combination with a metal ion complexing agent, such as crown ether or tetrabutylammonium salts [10].

### 7.4.1 Contaminants in the Water

The water target can be made of a variety of metals. The most common are silver, titanium and niobium. Some of advantages and disadvantages of these materials are given in Table 4.

TABLE 4. COMMON MATERIALS USED FOR CONSTRUCTION OF WATER TARGETS (SCHMITZ)

| Material properties | Ag | Ti | Nb |
|---|---|---|---|
| Chemical resistance | poor | good | good |
| Thermal conductivity (W/cm-K) | 4.29 | 0.219 | 0.537 |
| Radioisotopes from the target body | Cd-109 | V-48 | none |
| Reactivity of $^{18}F$ produced | average | good | good |
| Maintenance frequency | high | medium | low |

| Target pressure | low | medium | high |
|---|---|---|---|
| Maximum beam current (limit by target design and thermal conductivity) | 70 | 55 | 100 |

In the silver target, especially, there are colloids formed which can plug transfer lines. An example of the silver colloid deposited on the inside of a target foil is shown in Figure 4.

*FIG. 4. An example of silver colloid being deposited from solution inside the front foil of a water target*

The colloidal silver must be removed by filtration at or near the target in order to avoid plugging the lines. The other metals have less of a problem with this phenomenon, but may introduce metal impurities into the water which can interfere with the reactivity of the fluorine. The advantages and disadvantages of each of these materials can be weighed to a particular situation to decide which may be better.

### 7.4.2 Water Transfer

The transfer of $^{18}$O-enriched water through long lengths of small diameter (1/16”) tubing has been studied [11]. A single bolus of water was easily able to pass through the tubing. In this case, the transfer gas pressure only has to overcome two components due to surface tension acting at the two liquid-air interfaces at the beginning and end of the bolus. That is:

$$P > F1 + F2$$

Where:

- P is the force required to move the water through the tubing
- F1 and F2 are the two components due to surface tension.

It is found that with less controlled target emptying, the bolus of water is broken into 2 or 3 segments. The more segments, the slower the transfer through the tubing and a higher gas pressure is required. As the single bolus breaks up into many pieces, there are a greater number of components (due to surface tension) that the transfer gas pressure has to overcome. For example, for n components:

$$P > F1 + F2 + F3 + F4 + \ldots F2n$$

At higher pressures, the back end of the bolus tends to break up, leaving a small number of small droplets in the tubing. This effect is also seen when contaminated $^{18}$O-enriched water is used or when cleaning solvents are not completely removed from the tubing. Once the small droplets are present in the tubing, a bolus of water has a tendency to break up into segments, even when slow controlled transfer conditions are used. When the number of segments in the tubing becomes too great, the transfer gas pressure cannot overcome the surface tension of the combined segments. Increasing the transfer gas pressure only squeezes the segments closer together rather than continuing to push the water through the tubing.

If extreme pressure is used to force the water through the tubing, a fine coating of small droplets forms inside the tube. If another bolus is put through the tubing, it will not pass through the tubing without severe segmenting. Further drying of the line does not remove these droplets effectively. The only solution to remove the small droplets is to wash the lines with a suitable solvent miscible with water and then dry the lines thoroughly with air.

Another effect is seen when the previous emptying process is incomplete (i.e. water left behind in the tubing). A bolus of water from the current transfer can displace a bolus of water from the previous transfer. At the end of the transfer, the bolus of water from the previous transfer will arrive at the cell with the bolus from the current transfer remaining in the tube. It will appear that the target has emptied, but in reality, the radioactivity will be stuck in the lines, implying that there has been a target failure rather than a transfer problem. Only by thoroughly cleaning the lines can the transfer be returned to its normal operation.

There are a few solutions to this problem of water transfer. One is to extract the fluorine-18 from the water near the target and avoid long distance transfer of the enriched water. The other, less robust solution is to filter the water near the target with a fine polyethylene filter before passage through the tubing. This method also requires careful control of the pressure used to unload the target and frequent cleaning of the transfer lines.

### 7.4.3 Extraction

The most common method for the extraction of F-18 from an aqueous solution of $[^{18}O]H_2O$ is with the use of a anion exchange resin. The resins commonly in use are the Dowex1X8 resin in the carbonate form and the quaternary methyl amine (QMA) resin cartridge supplied by Alltec [7-9]. Once the F-18 has been extracted from the resin, it can be mixed with acetonitrile and transferred through fine bore tubing. The presence of acetonitrile reduces the surface tension of the water and allows a smoother transfer without the problems mentioned above. However, the bolus may still break up into pieces and some of the liquid and activity will be left on the inside of the tubing. One solution is to use a second rinse of pure acetonitrile to help remove the remaining activity. A schematic diagram of a water recovery system incorporating these features is shown in Figure 5 [12].

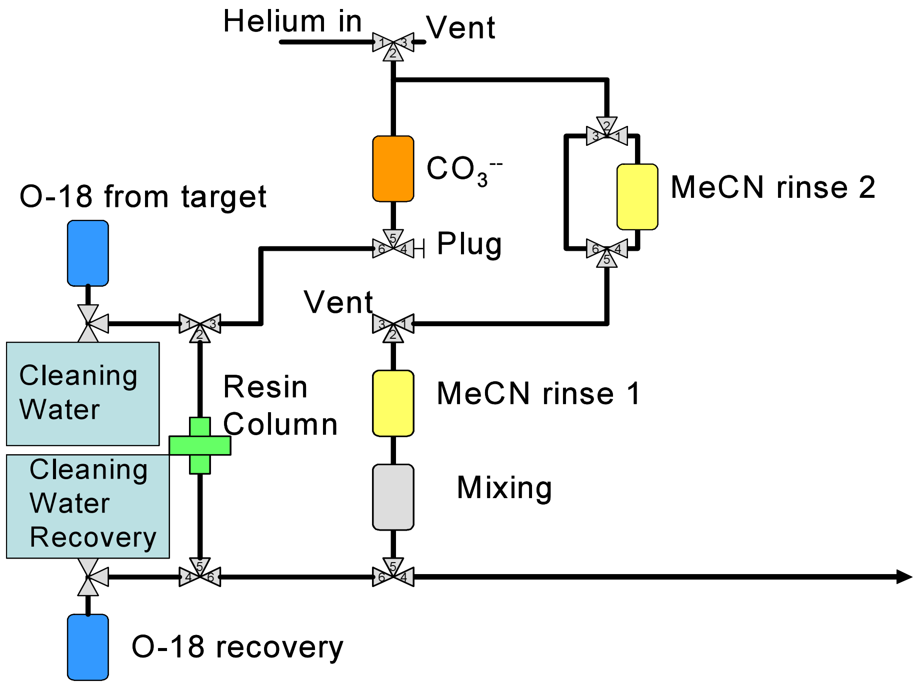

*FIG. 5. Schematic diagram of a resin system for recovery and elution of fluorine-18*

In this system which consists of four six-way valves, the water from the target is passed through the resin column and the O-18 water recovered in the O-18 recovery reservoir. The column is then switched and the carbonate reservoir empties through the resin column into the mixing reservoir. Acetonitrile is added to this reservoir and the resulting mixture is transferred through a long line to the Chemistry Lab which is 50 meters away. A second rinse of pure acetonitrile is passed through the line and is used to rinse any residual fluoride from the tubing. This second rinse typically recovers about 20% of the activity.

### 7.4.4 Distillation

If the water is to be reused, it must be distilled before being irradiated a second time. Fractional distillation is the common method and will remove many impurities and any metal radioisotopes which may have been introduced during irradiation. It is also important to maintain the pH of the water near 7.0. If the water becomes acidic, fluorine-19 ions can distill over with the water. One method to keep the pH high is to add a very small piece of sodium metal (carefully cleaned of all oil) to the water before distillation. This will raise the pH and not introduce any isotopic dilution to the enriched water.

### 7.4.5 Quality Control of Oxygen-18 Water

Oxygen-18 enriched water, after passing through an AG-1-X8 column in carbonate form, can become contaminated with amine residues from the resin. If acetonitrile is used in the extraction process, the water can be contaminated with the organic residue [11]. Fractional distillation of the recovered oxygen-18 enriched water will not effectively separate these impurities. Distillation from potassium permanganate and potassium hydroxide or other treatments to remove organic molecules may improve the purity of the water. After 2 - 3 distillations, the build up of impurities in the enriched water can become significant and may cause the break up of $^{18}$O-enriched water in the target empty lines. The organics can be removed from the water by UV irradiation and filtering or treatment with potassium permanganate. The water can also be cleaned by passage through an activated charcoal filter, but significant amounts of enriched water will be lost in this purification process.

The best solution is never to expose the resin to any organic solvents. If acetonitrile is added to aid in the transfer of the water over long distances, it should be added downstream of the resin column. Alcohol or acetone should never be used to clean the resin system, unless the entire apparatus can be taken apart and completely dried.

*Testing for organic impurities*: Organic impurities in the enriched water can be identified by passing the water through a gas chromatograph with a flame ionization detector. For most common impurities a 4.3 meter 80-100 mesh Porapak Q column at 135°C can be used [13].

*Removal of fluoride*: One method to remove the fluoride from the water is to distill from a basic solution as was described in section 7.4.4. The fluoride ion will stay in the reservoir and will not distill into the receiver vessel. This should also improve specific activity of the fluorine-18.

### 7.4.6 Maintenance Schedule for Water Targets

There should be a routine maintenance procedure established and followed for the target processing and quality control. Table 5 gives a suggested schedule for the maintenance [11].

TABLE 5. SUGGESTED MAINTENANCE SCHEDULE FOR $^{18}$O WATER TARGETS

| | |
|---|---|
| Weekly | Visually check for damaged tubing<br>Leak test the system<br>Prepare fresh O-18 water for use<br>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<br>Back-flush valves and check operation<br>Track target yields to establish trends |
| 6 months | Clean target<br>Replace all foils<br>Replace plastic parts if any degradation |
| General | Refrigerate O-18 water<br>Use sterile needles |

## 7.5 SOLID TARGET RECOVERY

It is often difficult to separate the product radioisotope from the target material in the solid phase. There are several techniques which may be applied. Three separate techniques are described here in some detail as examples.

The first is the solvent extraction method for $^{201}$Tl, given in section 7.5.1; the second is the thermal diffusion technique described in section 7.5.2 for $^{211}$At; and the third is electrochemical recovery of thallium given in section 7.6.

### 7.5.1 Solvent Extraction

One of the classical methods of extraction of radioisotopes from targets is solvent extraction [14-16]. In this technique, the entire target is dissolved in some solvent (usually an aqueous solution of either acid or base) and the radioisotope is extracted by using an organic solvent. Certain compounds of some elements, under the proper conditions, will preferentially transfer from the aqueous phase into immiscible organic solvents. Some solvent extraction processes are highly specific. Another technique is chelation of the metal ions. It is usually possible to alter the conditions of the solvent extraction system so that the desired element passes back into the aqueous phase. This 'back extraction' may act further to increase the specificity of the solvent extraction operation, as well as to return the substance under investigation to a more convenient medium for further purification. Below is an example of the solvent extraction for the production of $^{201}$Tl. The $^{201}$Pb is made from the $^{203}$Tl(p,3n)$^{201}$Pb nuclear reaction [17]. The target is usually a copper plate with the thallium-203 target material electroplated. After irradiation the $^{201}$Pb must be extracted from the target plate. There are two steps in this procedure. The first is the separation of the $^{201}$Pb from the target plate and the second is the separation of the $^{201}$Tl which has grown in from the $^{201}$Pb.

#### *7.5.1.1. Step1. Separation of $^{201}$Pb from $^{203}$Tl target plate:*

- $^{203}$Tl target is dissolved in 2-4 mL of 4M sulfuric acid. This will dissolve the thallium without dissolving much of the copper plate. A barrier or hold is used to protect the copper plate from the sulfuric acid.
- The dissolved target material is transferred into a flask and target plate is rinsed with dilute sulfuric acid, this solution is also added to the flask.
- Aqua regia (20 mL conc. HCl + 3 mL conc. nitric acid) is added to the flask to convert all the thallium into the thallic (+3) oxidation state.
- The solution is transferred to a separatory funnel and mixed thoroughly by bubbling with a stream of filtered air. This ensures that all the thallium will be in the higher (+3) oxidation state.
- 50 mL of n-butyl acetate equilibrated with 6M HCl, is added to the separatory funnel, and the two phases mixed well by bubbling with the air stream.
- After separation of phases, the aqueous layer containing the $^{201}$Pb is collected into a clean quartz beaker.

- The organic phase is extracted again with two 5 mL portions of 6 M HCl, collecting the aqueous phase in the same beaker. The same procedure, using an air stream to mix and equilibrate the phases, is done.
- The aqueous layer containing all the $^{201}$Pb is transferred to another separatory funnel.
- Any residual chemical $^{203}$Tl is now removed by repeated extractions with n-butyl acetate. This $^{203}$Tl will later be recovered from the organic phase for reuse.
- The aqueous phase is collected in flask containing 3 mL of conc. nitric acid.
- The aqueous phase should be tested for $^{203}$Tl in the $^{201}$Pb solution at this stage to ensure compliance with required chemical purity of the $^{201}$Tl bulk; if no $^{203}$Tl is detected in the solution, it should be set aside for $^{201}$Tl to grow for ~32 hours.
- The n-butyl acetate phase containing enriched $^{203}$Tl is set aside for recovery at a later stage.

#### *7.5.1.2. Step 2. Separation of $^{201}$Tl from $^{201}$Pb:*

- After sufficient $^{201}$Tl growth period, the solution is transferred to a separatory funnel.
- The 50 mL of DIPE (diisopropyl ether) equilibrated with 6M HCl is transferred to the extractor and phases are mixed well with stream of filtered air.
- The aqueous phase containing $^{201}$Pb is removed, and the organic phase is washed two times with 20 mL of 6.0 M HCl to remove residual $^{201}$Pb.
- The $^{201}$Tl is back extracted into aqueous phase in two portions of 10 mL each of sterile water saturated with $SO_2$ gas (the mild reducing agent will convert the oxidation state from thallic (+3) into thallous (+1)).
- The combined aqueous phase containing the $^{201}$Tl is carefully evaporated to dryness.
- The $^{201}$Tl activity is dissolved in 0.9% NaCl solution, the solution is then filtered, and the quality testing is carried out.

Some difficulties may arise in solvent-extraction such as emulsion formation or the slow attainment of equilibrium. The organic phase may extract enough of the reagents from the aqueous phase to alter the original conditions of the extraction. There may be a tendency for radiocolloidal impurities, not in themselves extractable, to collect on the interface between the phases. Substances which extract in macro amounts may not extract as readily in trace quantities.

### 7.5.2 Thermal Diffusion

One of the more common methods for the separation of radioisotopes from solid targets is thermal diffusion, which is also known as dry distillation. In this technique, a solid target is heated to a temperature where the radioisotope can be volatilized but where the target material does not diffuse away from the target. This technique is common for radiohalogens because of the relative volatility of the halogen when compared to the target material. The dry distillation system for the isolation of $^{211}$At from the bismuth cyclotron target is shown in Figure 6 [18].

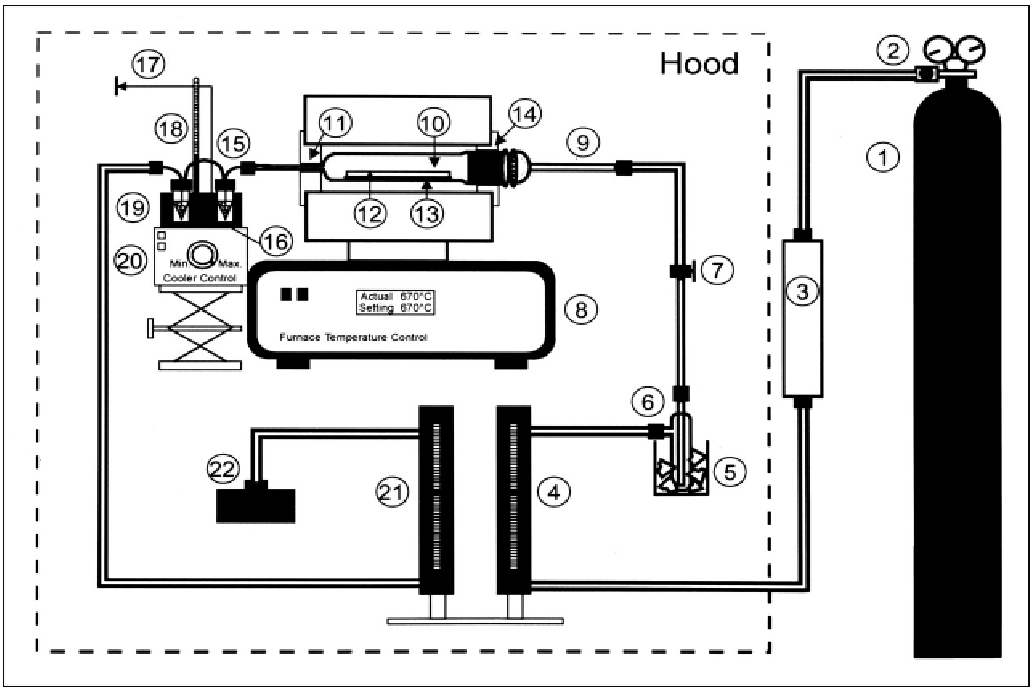

*FIG. 6. The Distillation Apparatus Used for Isolation of $^{211}$At from Bismuth Cyclotron Target.*

Where:

(1) Argon Cylinder, (2) Argon Gas Regulator, (3) Gas Filter, (4) Inlet Flow Meter and Valve, (5) Dewar Containing Dry Ice, (6) Ether Trap, (7) Teflon Valve, (8) Tube Furnace, (9) Quartz Inlet Tube, (10) Quartz Still, (11) Insulation Ring, (12) Aluminum-Backed Bismuth Cyclotron Target, (13) Quartz Support Plate, (14) Insulation Ring, (15) Glass Still Outlet Tube, (16) Radioactivity Detector, (17) Detector Output to Amplifier, Counter, and Strip Chart Recorder, (18) Thermometer, (19) Aluminum Cooling Block, (20) Thermoelectric Cooler, (21) Outlet Flow Meter, and (22) Charcoal Filter Trap [18].

The efficiency of the recovery for this type of thermal diffusion varies depending on a number of factors which include the relative vapor pressures of the target and product. For $^{211}$At, the extraction has been reported anywhere from 45% up to 75%. A typical procedure for the thermal diffusion method is given below.

Prior to each distillation, the quartz and glassware components of the distillation apparatus were cleaned as follows: 1) soaked in concentrated $HNO_3$ for at least 5 hours; 2) rinsed in cold water; 3) soaked in hot soapy water (Alconox, New York, NY) for 30 minutes followed by brush-washing; 4) rinsed with cold tap water and, finally, distilled water; and 5) baked in an oven for at least 12 hours at 120°C. Before each distillation, the still and condensing unit were assembled and inserted into the furnace and heated to 150-200°C under a flow of argon [19]. The target is removed from the cyclotron and transferred to the hot cell containing the distillation apparatus. A flow of argon is started in the apparatus through the dry ice trap to remove any traces of water and the furnace turned on. After insertion of the target in the apparatus, the temperature of the plate is brought up to the desired distillation temperature of 670°C.

The distillation is terminated when a plateau in activity, determined by the scintillation detector, has been reached (usually about 20 to 30 minutes). In this operation, the $^{211}$At is trapped by condensation in two gas-washing bubbler traps of approx. 2 mL volume (near 16 in Figure 6) in series, to which is added 300/µL of the desired solvent for collection of the distilled $^{211}$At. During distillations, the bubbler traps are cooled with ice [18].

## 7.6 DISSOLUTION OF THALLIUM-201TARGETS

Irradiated thallium targets can be dissolved in diluted nitric acid, sulfuric acid or in concentrated hydrogen peroxide.

### 7.6.1 Classical Methods

There are several classical methods for the dissolution of the $^{203}$Tl target. An automated device for this dissolution is shown in Figure 7.

*FIG. 7. Manifold for Dissolution and Precipitation of the Target Material. Right Side of the Figure Shows a Close up of the Dissolution Plate Holder*

### 7.6.2 Flow through Stripper

Using a flow-through stripper that allows heating (70-80 °C) on the coolant side, the fast (10-15 minutes) solubilization in 20 to 30 ml 0.7N $HNO_3$ results in co-dissolution of milligram amounts of copper. Consequently, apart from the $^{203}$Tl and the lead and thallium radionuclides formed during the irradiation, the stripping solution will be contaminated with copper and some carrier free $^{65}$Zn.

When time-consuming (1 hour) dissolution in 4 to 5M sulfuric acid at room temperature is performed, only microgram amounts of copper are dissolved. Though attractive from analytical point of view, the sulfuric acid dissolution will give rise to a loss of about 10% of the Tl-201 during the solubilization step. Heating up to 60-70 °C and vigorous stirring will increase the dissolution rate but will also result in a higher copper and zinc-65 contamination. Appropriate chemical processing is then a must. The dissolution in $H_2O_2$ is done by drop by drop moistening of the thallium. This step gives rise to a violent auto-catalytic oxidation reaction resulting in the formation of a dark-brown to black slurry consisting of a mixture of thallium hydroxides. The latter are readily dissolved and the thallium reduced to the monovalent oxidation state in 1N hot perchloric acid.

Chemical processing involves two steps, the fast separation of $^{201}$Pb from irradiated and dissolved $^{203}$Tl target material (Chemistry-1) at the end of the bombardment and the separation of non-carrier added $^{201}$Tl from the remaining $^{201}$Pb (Chemistry-2) after an appropriate grow-in period (25 to 35 hours). It should be noted that only about 90% of the $^{201}$Pb has decayed into $^{201}$Tl at the moment. Re-extraction of $^{201}$Tl from the resulting lead solution after a second decay period may increase the $^{201}$Tl yield by more than 5%.

Many radiochemical procedures for preparation of good quality $^{201}$Tl bulks are available in the literature [20, 21]. For Chemistry-1 precipitation ($PbSO_4$ after addition of lead carrier), co-precipitation (with $Fe(OH)_3$, $SrSO_4$), anion and cation exchange chromatography, and adsorption chromatography are frequently applied. Chemistry-2 often involves a two-step separation: chromatography for the separation of monovalent $^{201}$Tl after reduction (with $SO_2$) from the $^{201}$Pb bulk (upon decay of lead into thallium a mixture of mono- and trivalent thallium is obtained) and chromatography and solvent/solvent extraction of trivalent $^{201}$Tl (oxidation with $KbrO_3$, $O_3$ gas). Upon reduction (with $SO_2$ and $NaHSO_3$); back-extraction is performed followed by $^{201}$Tl bulk conditioning (pH and isotonicity adjustment, sterilization). Some examples are summarized in Table 6 (Procedures for $^{201}$Tl production) and Table 7 (Typical $^{201}$Tl Yield).

TABLE 6. PROCEDURES FOR THALLIUM-201 PRODUCTION IN DIFFERENT INSTITUTIONS

| Institute | Dissolution Tl-203 | Chemistry 1 |
|---|---|---|
| NRCAM<br>VUB | 0.7N $HNO_3$<br>Flow-through stripper at 60-70 °C | Precipitation $PbSO_4$<br>Redissolution in EDTA (pH =5)<br>Cation exchange to remove co-precipitated Tl-203<br>$^{201}$Pb/EDTA bulk solution decay |
| C.N.E.A. | 0.7N $HNO_3$<br>Bulk dissolution at room temperature | Cationic exchange 0.1M $HNO_3$<br>$^{201}$Pb decays on column |
| I.N.P. | 5M $H_2SO_4$<br>Bulk dissolution at 80 ºC | Co-precipitation with $SrSO_4$<br>$^{201}$Pb decays adsorbed at precipitate |

TABLE 7. TYPICAL $^{201}$Tl YIELD

| Institute | Chemistry 2 | $^{201}$Tl yield |
|---|---|---|
| NRCAM<br>VUB | Reduction $SO_2$, Cation exchange (0.1M EDTA)<br>Elution $^{201}$Tl (6N HCl),<br>Oxidation ($O_3$), Extraction DIPE,<br>Reduction ($SO_2$), back-extraction 0.01M HCl | 1-1.5 Ci |
| C.N.E.A. | Elution of $^{201}$Tl (0.1M HCl) | 1.2-1.6 Ci |
| I.N.P. | Redissolution (6M HCl),<br>Oxidation ($KBrO_3$)<br>Solvent extraction (Butyl–acetate )<br>Reduction ($H_2SO_3$), back-extraction (0.01M HCl) | 300 mCi |

The precipitation of $^{201}$Pb can be carried out using the apparatus shown in Figure 8.

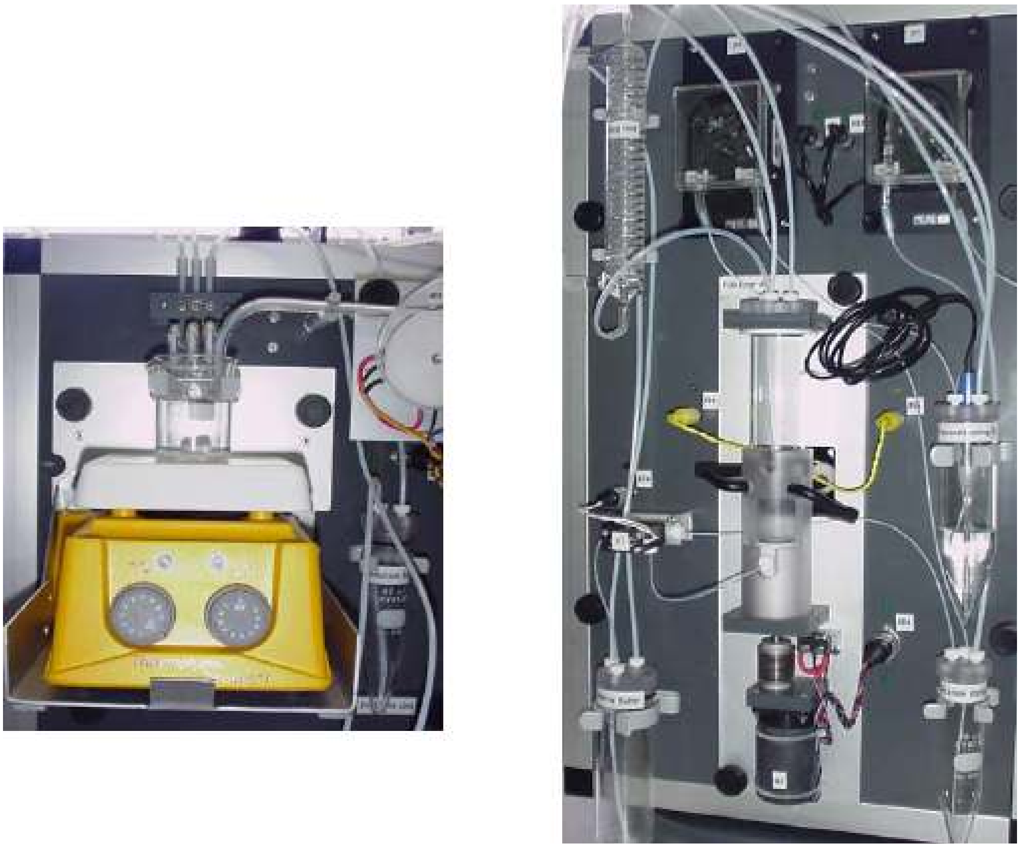

*FIG. 8. Manifold used for the precipitation of $^{201}$Pb (left) and the filtration of the final solution (right)*

It is possible to use electrochemical techniques to perform all the tasks associated with the preparation, recovery and separation of targets for producing radioisotopes. As was mentioned before, this is a separation of metals by controlled cathode potential electrolysis (CCPE)

In principle, we can perform the separation of metals by CCPE if their discharge intervals do not overlap. We can shift the interval for a given metal and hydrogen by the addition of appropriate complexing agents and pH-adjustment. The upper limit of the discharge interval can be determined from current-voltage curves, and the lower limit can be easily detected by current monitoring (exponential decrease).

As an example we can use the following conditions for the thallium solutions:

- Electrodes: Reference electrode $Hg/Hg_2SO_4$/sat $K_2SO_4$ (+412 mV) (Russell)
- Anode: Pt wire
- Cathodes: Cu deposition - Home made cylindrical Cu gauze
- Tl deposition: - Pt gauze (Johnson - Matthey)
- Zn deposition: - Home made cylindrical Cu gauze.
- The values of cathodic potential versus the reference for selective deposition.

These are the solution requirements for deposition of:

- Cu: Acid solution ($HNO_3/H_2SO_4$) at $1.5 < pH < 3$ with $N_2H_4$ depolarizer
- Tl: Alkaline (pH > 12) $Tl(EDTA)_3^-$ solution with $N_2H_4$ depolarizer
- Zn:Strong alkaline solution (pH >> 12)

The current voltage curves for these reactions are given in Figure 9.

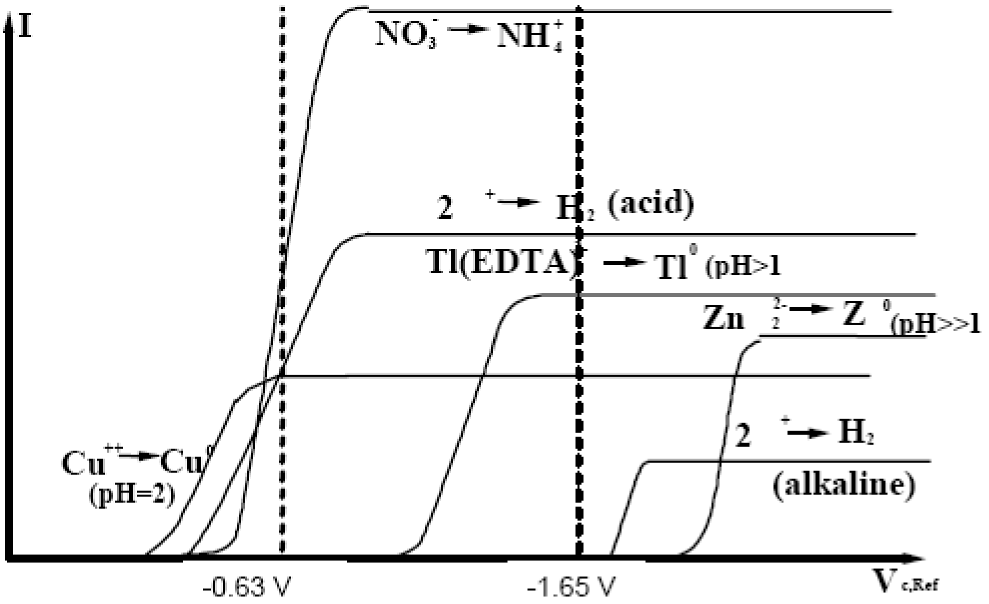

*FIG. 9. Current voltage curves and possible reactions*

### 7.6.3 Centrifugal Electrochemistry

There is a more recent technique developed to dissolve the target material which is especially useful for the dissolution of rhodium targets. This is the centrifugal electro-dissolution technology. It has several advantages which are:

- Limited Final Volume (± 40 ml)
- Quantitative dissolution (> 99 %)
- High current density (> 2 $A.cm^{-2}$)
- Time-controlled dissolution (rate)
- Suited for rhodium fragments, powder, cut wires & foils

The basic methodology is diagramed in Figure 10. It shows how the liquid level is raised and the solids are drawn away from the central electrode by the centrifugal forces.

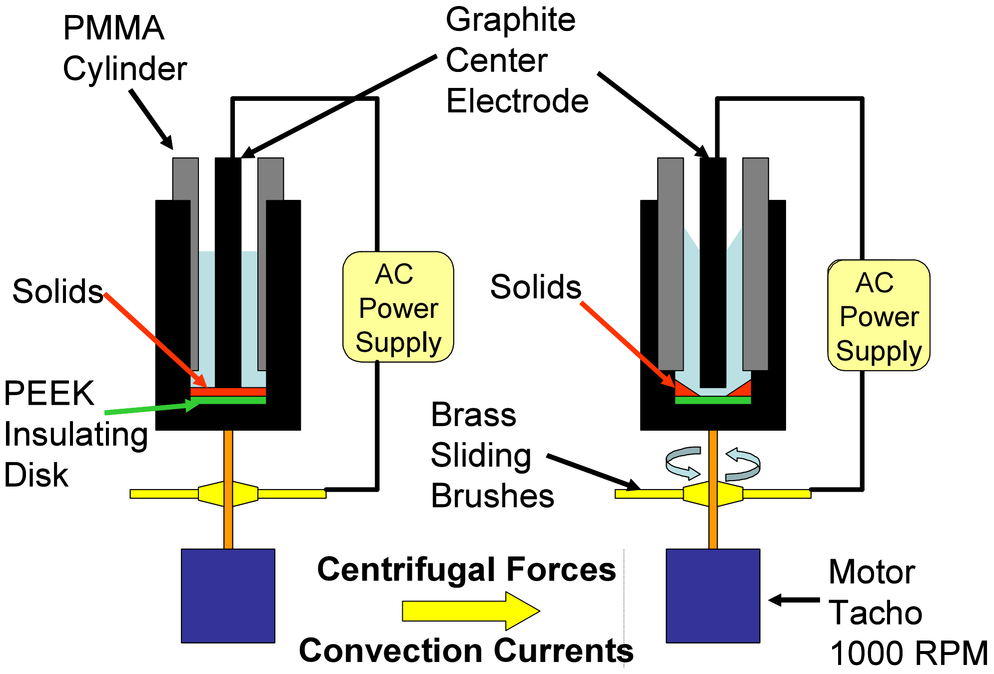

*FIG. 10. Schematic diagram of centrifugal electro-dissolution assembly*

## 7.7 RECOVERY OF MATERIAL FROM PLATING SOLUTIONS

One of the aspects of solid targets is to recover the enriched isotope used for the target. The following section describes the recovery of thallium-203 used to produce thallium-201 as an example for solid target recovery. Further examples may be found in the IAEA TRS 432: Standardized High Current Solid Targets for Cyclotron Production of Diagnostic and Therapeutic Radionuclides. Quantitative and rapid recovery of enriched Tl-203 from partially depleted plating baths or from recovery solutions can be achieved, using these methods [22, 23].

### 7.7.1 Recovery of Enriched Thallium

The CCPE method can be used to recover enriched thallium from partially depleted plating solutions (alkaline EDTA solutions containing thallium metal only) or from recovery solutions (nitric or sulfuric acid or alkaline ammonia nitrate solutions containing copper, thallium and carrier free zinc-65) obtained after processing of irradiated targets. This electro-separation technique is based on the shift of a metal ion discharge interval, and subsequent selective separation, by addition of complexing agents to, and/or pH adjustment of, a solution containing a mixture of metals. The method involves the use of a three-electrode set up: a cylindrical large area copper (or platinum) gauze cathode, a platinum wire anode mounted axially inside the cathode, and a reference electrode positioned close to the cathode. The electrode set is immersed in a properly adjusted recovery solution and connected to a potentiostat. This allows fixing the potential of the cathode versus the reference electrode to a value such that one metal is selectively and quantitatively deposited. Upon removal of the metal deposit from the cathode or upon introduction of a new cathode, the composition of the solution, and the potential of the cathode are changed such that a second metal can be plated out, and so on. The end of the deposition of a given metal is detected by monitoring the exponential current flowing through the cathode circuitry, current that should approach zero near the endpoint. The experimental conditions for the separation of copper, thallium and zinc are summarized in Table 8. Up to 15 g of enriched $^{203}$Tl may be recovered in a single run.

TABLE 8. ELECTRO-SEPARATION OF COPPER, THALLIUM AND ZINC; REFERENCE ELECTRODE: HG/$HgSO_4$/SAT $K_2SO_4$ (+412 MV VS NHE)

| Element | Solution | pH | Cathode | Ecathodevs Ref |
|---|---|---|---|---|
| Cu | $HNO_3/H_2SO_4$ | $1.5<pH<3$ | Cu-gauze | - 0.630 |
| Tl | EDTA | >12 | Pt-gauze | - 1.650 |
| Zn | NaOH excess | >>12 | Cu-gauze | Constant current |

### 7.7.2 Separation of Copper

Copper may be present in the recovery solutions if nitric acid is used to dissolve the thallium layer. If dissolution of the irradiated target material is performed in sulfuric acid, this step may be skipped. This is also the case when recovery of thallium from partially depleted alkaline EDTA solutions is performed. To make the method applicable when the Tl-203/Pb-201 separation is done by co-precipitation of carrier free $^{201}$Pb with $Fe(OH)_3$ in alkaline ammonia nitrate medium, the procedure starts with the addition of concentrated ammonia to the nitric acid recovery solution.

### 7.7.3 Separation of Thallium

Upon removal of copper, the composition of the recovery solution is altered such that it approaches the plating bath described in Chapter 6. $^{203}$Tl is selectively plated out on a large area platinum gauze electrode. The thallium can be re-dissolved in diluted sulfuric acid containing a minor amount of hydrogen peroxide. The peroxide helps to increase the dissolution rate. The solution thus obtained can be used to prepare a new plating bath.

### 7.7.4 Separation of Zinc

Although it is of no practical concern for radionuclide production itself, $^{65}$Zn is plated out on the copper gauze electrode after the addition of a suitable amount of carrier. This is done solely to avoid making a large-volume of long-lived liquid waste, the disposal of which is very expensive. Pressing together the copper gauze after the zinc plating, one can obtain less than 1 cm$^3$ of solid waste. As the precious enriched $^{203}$Tl has been removed in the preceding step, constant current electroplating at high current density can be applied.

## 7.8 SYNTHESIS OF CARBON-11 COMPOUNDS

For Carbon-11, the molecule that is the most stable in an oxidising environment is $CO_2$. In a reducing environment, the most stable is usually methane ($CH_4$). Either of these two chemical forms are the building blocks of more complex molecules.

### 7.8.1 Carbon-11 Carbon Dioxide

Carbon-11 is most commonly produced in a $N_2$ gas target using the $^{14}N(p,\alpha)^{11}C$ nuclear reaction. A trace of oxygen is added to convert all the $^{11}$C into $CO_2$. Almost all syntheses involving $^{11}$C start with $CO_2$ as the primary product.

A number of other precursor molecules, some of which are shown in Figure 11, are synthesised from labelled $CO_2$, but all require some synthetic manipulation during or after cyclotron bombardment [13, 24-26].

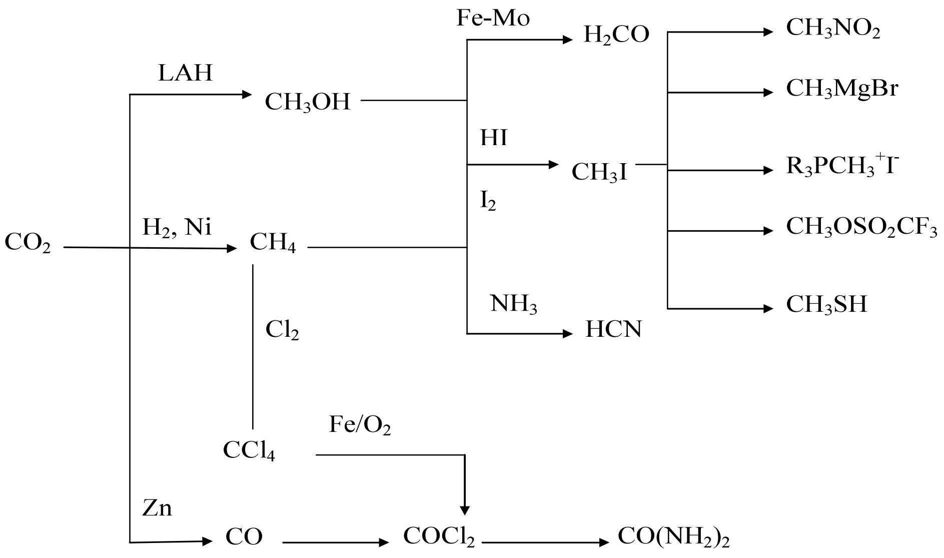

*FIG. 11. Reaction pathways for the synthesis of $^{11}C$ precursors*

### 7.8.2 Commercial Boxes for Synthesis

There are many commercial boxes for the preparation of carbon-11 molecules. Excellent reviews have been written which give the characteristics of these synthesis modules [27, 28]. Although automated chemistry systems for PET radiopharmaceuticals have a wide variety of designs, they also have some common characteristics. All of these systems were created using the modular design concept of laboratory unit operations [29, 30]. Each radio-synthesis can be broken down into a set of common laboratory operations. In radiotracer synthesis, these general-purpose operations include manipulations common to the organic chemist, i.e. transferring reagents, evaporating solvents, regulating vessel temperature, and solid phase extraction (SPE). Unit operations design was first successfully applied to the design of remotely controlled syntheses of several carbon-11 tracers [31, 32, 29]. It is a useful engineering concept that has also been applied successfully to both robot systems [33-35] and fixed plumbed 'black-box' automation [36]. Structured design techniques facilitate the development of automated systems from manual methods by first providing plumbing building blocks for remotely-controlled systems [37, 28] and then providing a framework for both process control system and software design [38, 39].

## 7.9 SYNTHESIS OF FLUORINE-18 COMPOUNDS

In the case of $^{18}F$, the usual product out of the target is usually either fluoride ion ($F^-$) or fluorine gas ($F_2$), depending on the environment in the target during irradiation.

### 7.9.1 Synthesis of FDG

The most widely used fluorine-18 containing compound by far is 2-deoxy-2-[$^{18}F$]fluoro-D-glucose ($^{18}FDG$).

It was developed in 1976 in a collaborative effort between scientists at the National Institutes of Health, the University of Pennsylvania, and Brookhaven National Laboratory [40]). It was developed for the specific purpose of mapping brain glucose metabolism in living humans, thereby serving as a tool in the basic human neurosciences.

With $^{18}$FDG, it was possible for the first time to measure regional glucose metabolism in the living human brain. During that same period, the uses of $^{18}$FDG for studies of myocardial metabolism and as a tracer for tumor metabolism were reported. After the first synthesis of $^{18}$FDG via an electrophilic fluorination with $^{18}F_2$ gas (produced via the $^{20}Ne(d,\alpha)^{18}F$ reaction), small volume enriched water targets were developed that made it possible to produce large quantities of [$^{18}$F]fluoride ion via the high-yield $^{18}O(p,n)^{18}F$ reaction. A major advance in the synthesis of $^{18}$FDG from [$^{18}$F]fluoride was reported in 1986 when it was discovered that kryptofix 222 could be used to increase the reactivity of [$^{18}$F]fluoride [10]. In essence, kryptofix masks the potassium ions, which are the counter-ions of the [$^{18}$F] fluoride. The reaction of [$^{18}$F]fluoride with 1,3,4,6-tetra-O-acety1-2-O-trifluoromethanesulfony1-2-O-mannopyranose to give 1,3,4,6-tetra-O-acetyl-2-[$^{18}$F]fluoro-D-gluco-pyranose gives a 95% incorporation of $^{18}$F, and the overall synthesis, including purification, proceeds with about a 60% yield. The synthesis involves 2 steps; displacement with [$^{18}$F]fluoride, and deprotection with HCl or NaOH. This new method served an increasing need in the nuclear medicine and the neuroscience communities, which were discovering new uses for $^{18}$FDG. It is also simple and amenable to automation and in the 20 years since it was reported, a number of automated synthesis modules have become commercially available.

### 7.9.2 Synthesis of Other Fluorine Containing Compounds

In nucleophilic fluorination, $^{18}$F labelled fluoride ion is almost always obtained as an aqueous solution. Fluoride ion is quite unreactive and requires some simple, but very important, manipulations to become a reactive nucleophilic reagent. A great deal of work has gone into developing methods for the preparation of reactive fluoride ion in organic solvents suitable for chemical syntheses. The steps in preparing reactive fluoride are crucial to the success of the labelling reactions and it is worthwhile to examine the methods commonly being used.

In any aqueous solution, the fluoride ion must be accompanied by positively charged counter ion. As the fluoride is removed from the target, the metal ions in the water, which were rinsed off the surface of the target during irradiation, probably serve this purpose. The reactivity of the fluoride is very effectively enhanced by the addition of a cationic counter ion prior to the evaporation of the water. Three types of counter ions have been used: large metal ions, such as rubidium or cesium; potassium complexed by a cryptand, such as Kryptofix 222 [10]; or tetrabutylammonium salts [41]. Most syntheses now utilize the Kryptofix system or tetrabutylammonium salts. The addition of a cation also involves the inclusion of another anion to the reaction mixture. Anions such as hydroxide or carbonate are used, which do not effectively compete with the fluoride ion in nucleophilic displacement reactions. Carbonate is usually the anion of choice since it is less likely to cause base-catalysed side reactions.

#### *7.9.2.1. Aliphatic Nucleophilic Displacements*

The reaction of [$^{18}$F] fluoride ion with various leaving groups is an excellent method for the synthesis of aliphatic carbon-fluorine bonds [42]. The choice of leaving group will depend on the yield, stability of precursors, ease of subsequent separation of the [$^{18}$F]fluorinated product from precursors, reagents and solvents, and the formation of potential side products [43].

#### *7.9.2.2.Aromatic Nucleophilic Substitution*

Fluorine-substituted aromatic rings are common in many types of biologically active organic molecules. Fluorine is similar in size to the hydrogen atom and does not have serious steric effects, but its high electronegativity can significantly alter the electronic characteristics of the aryl ring. Nucleophilic aromatic substitution, where $^{18}$F is substituted for a leaving group, has become a method used widely in $^{18}$F chemistry [44]. Nitro and trimethylammonium groups are the most widely used leaving groups in aromatic substitutions with [$^{18}$F]fluoride ion [45].

Simple isotopic substitution of [$^{18}$F]fluoride for [$^{19}$F]fluoride can be an effective method for synthesis of a new radiotracer. The low specific activity necessitated by these isotopic substitutions makes this reaction possible only when the specific activity of the final product is not important.

### *7.9.2.3. Electrophillic Reactions*

Various electrophilic fluorinating agents have been developed for use in the synthesis of radiotracers for PET. The first to be used was $F_2$ derived directly from the irradiation of neon [46]. The problem was that fluorine will react with nearly everything and the highly exothermic reactions must be controlled, either with low temperature or by using very dilute solutions of fluorine in an inert solvent. The solution to this problem was to convert the fluorine into a slightly less reactive form, such as acetyl hypofluorite [47] or xenon difluoride [48]. Since all of these reagents must be prepared using carrier fluorine, the specific activity of the final product is always low. Despite these drawbacks, electrophilic fluorinations have played a vital role in the development of the radiotracers used for PET. Both FDG and Fluoro-DOPA were first prepared using this method. F-DOPA is still routinely prepared with electrophilic fluorination.

### 7.9.3 Commercial boxes for synthesis

The synthesis of $^{18}$F-fluorodeoxyglucose (FDG) involves the production of $^{18}$F-fluoride followed by reaction with mannose triflate and subsequent de-blocking of the protected sugar resulting in the production of the $^{18}$F-FDG. These steps are generally accomplished with one of several commercially available synthesis systems. The efficiency for the conversion of the label typically varies between 50 and 70%. The cause of this variability is not completely understood. A study was carried out determining the efficiency of $^{18}$F-FDG production from three commercially available automated synthesis systems [49]. All synthesis systems made use of the Hamacher [10] method where $^{18}$F-fluoride (fluoride) displaces the triflate-leaving group and the labeled acetylated fluorodeoxyglucose is then de-blocked using either HCl or NaOH. The yields were determined by comparing the quantity of $^{18}$F-fluoride at the start of synthesis and the quantity of FDG produced at the end of the synthesis. The synthesis systems used included the CTI-CPCU unit at the PETScan Centre in Vancouver, British Columbia, Canada, the EBCO system at the Vancouver Hospital also in Vancouver, and the Coincidence Box at the Cross Cancer Centre in Edmonton, Alberta, Canada. In addition to these studies, another set of studies at Memorial Sloan Kettering Cancer Center compared two different GE MicroLab FDG synthesis units.

From these results it appears that the commercially available synthesis units tested provide similar yields of FDG with comparable quality of final product. While the results from Vancouver General Hospital appear a little lower than the other two sites, the number of runs is small and the uncertainties associated with these results certainly overlap with those of the other units.

However, the efficiency of FDG production appears to be dependent upon the source of $^{18}$F-fluoride. The yields using the same synthesis system (at PETScan) gave statistically significant different results for the two sources of $^{18}$F-fluoride, while the yield on the coincidence box were nearly identical using 2 different sources of fluoride. However, the target systems for the production of fluoride both made use of a niobium target body, although of completely different configuration. The $^{18}$F-fluoride produced in the niobium target body provides higher yields than a silver target body. The reason(s) for this difference is not understood. Another possibility is the purity of the target material ($H_2{}^{18}O$) for producing the $^{18}$F. It should be noted that some commercial manufacturers claim to have >65% FDG yield for in-house productions which implies that the target and water are not the source of the yield problems. Shipping long distances does not appear to affect yields since the Coincidence system's use of fluoride shipped as irradiated $H_2{}^{18}O$ (not loaded on an ion column) from TRIUMF in Vancouver (8 hours from EOB) as well as from their own cyclotron with similar yields.

Table 9 provides the decay corrected radiochemical yields of FDG from the various synthesis systems and $^{18}$F-fluoride from different target systems as noted in the text.

TABLE 9. DECAY CORRECTED RADIOCHEMICAL YIELDS OF FDG FROM THE VARIOUS SYNTHESIS SYSTEMS AND $^{18}$F-FLUORIDE FROM DIFFERENT TARGET SYSTEMS AS NOTED IN THE TEXT

| Unit | D.C. Yield (%) ± Std. | n |
|---|---|---|
| CPCU –PETNet fluoride | 52.1 ± 7.2 | 32 |
| CPCU –TRIUMF fluoride | 62.0 ± 10.5 | 17 |
| EBCO - TRIUMF fluoride | 57.4 ± 2.8 | 8 |
| Coincidence - TRIUMF fluoride | 65.4 ± 4.4 | 34 |
| Coincidence- CCC TR19 fluoride | 64.7 ± 10.9 | 64 |

The results from Sloan Kettering are shown in Table 10 [50]. All of the values in the table are the percentage of fluorine-18 activity at the start of synthesis.

TABLE 10. YIELDS FROM TWO GE MICROLAB FDG SYNTHESIS BOXES USED IN THE SAME LABORATORY DEMONSTRATING THE REPEATABILITY

| Parameter | Box A | Box B |
|---|---|---|
| FDG Yield (%) | 63.4 ± 5.8 | 62.9 ± 4.6 |
| Activity left on the reaction column (%) | 9.3 ± 3.1 | 8.4 ± 2.5 |
| Activity left on the alumina column (%) | 4.0 ± 0.6 | 2.6 ± 0.6 |
| Activity left on the C-18 column (%) | 8.9 ± 1.0 | 9.5 ± 1.5 |

There were two other important observations made in this study. The first was that there was very little degradation in the cassettes as they were stored beyond 150 days, and the second was that the yield was not very dependent on the level of starting activity up to 500 mCi.

## 7.10 CONCLUSIONS

The processing of the target after irradiation is a critical part of the radioisotope production process. The separation of the product from the target material and the recovery of any enriched isotope target material are critical to the overall success of a facility. The conversion of the chemical for the radioisotope to a useful precursor can be a complex process as in the case of some carbon-11 precursors, or a very simple matter as is the case of fluoride, where the product can be used with almost no further processing.

The electrochemical recovery of solid target material offers several advantages over other methods and the yields for these recoveries can be very high (>98%). The recovery of the $^{203}$Tl given as an example has dramatically simplified the processing, which must be done after the plating solution is depleted.

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# 8 FUTURE DIRECTIONS

## 8.1 INTRODUCTION

Ever since the invention of the cyclotron by Ernest Lawrence, there has been a steady progress at various fronts in this field. In this book, Cyclotrons, their characteristics, and theory and practice of producing radioisotopes with the cyclotrons have been reviewed. The important aspects of isotope production including, targetry and irradiation of the targets for most efficient production of isotopes have been discussed. Applications of radioisotopes produced in a cyclotron are wide ranging, and are limited only by the imagination of the user. As a cyclotron facility embarks upon production of multiple radioisotopes and radiotracers, there is a need to understand the underlying principles so that it becomes possible to design new targets and production and separation procedures which enhance the production of new radioisotopes. The availability of accelerators with ever increasing performance (beam current, energy), the increasing demand for widespread availability of valuable clinical pharmaceuticals and the pronounced trend towards miniaturization of equipment and electronics will undoubtedly affect the way in which the radionuclides will be produced (automated/manually, on-site/centralized, nuclide/nuclide generator, etc.)

## 8.2 TRANSLATIONAL SCIENCE

As in every field of science, radioisotope production is not a static endeavour. The advances in a number of areas will eventually impact the design of accelerators, their targets, the processing of these targets and how the desired radioisotopes are utilized. While it is impossible to use a crystal ball to foretell the future advances and directions, there are a few areas which are likely to impact the field of radioisotope production, either directly or indirectly. For example, the possibility of large-scale production of radioisotopes from photons seemed almost laughable a decade ago, while now that possibility seems, at least on the proof-of-principle level, highly probable. Further developments will depend upon the ability to shrink the size of the lasers and increase the frequency of pulse delivery. If this approach proves practical then there will be a concomitant need for new approaches to targetry to take advantage of this technology.

The advances in *nano* technology will impact the way in which radioisotopes will be incorporated into useful chemical entities such as biomarkers and radiotherapeutic agents. If the lab-on-a-chip approach becomes a reality for biomarker production, the miniaturization of the entire process will directly impact how the radioisotopes are produced and delivered. This in turn affects the design of targets and their operation.

## 8.3 CENTRALIZED RADIOISOTOPE PRODUCTION

In many Member States, it is likely that there would be only a single or very few accelerator facilities around the country. Considering the necessity of extensive resources required for such a facility, establishment of a centralized radioisotope production facility fulfilling the national needs may be an optimum situation for many Member States. This in turn implies that this facility must keep up with the current state of the art in radioisotope production and radiopharmaceutical development.

It should be understood that distribution of radioisotopes (or the radiopharmaceuticals) from a national accelerator facility represents the best use of precious resources. The longer lived radioisotopes would be relatively easier to transport to distant locations within the country. Radioisotopes with shorter half-lives present some logistical problems in distribution.

## 8.4 RADIOISOTOPES FOR GENERATOR PRODUCTION

The molybdenum/technetium-99m generator remains the dominant source for radionuclide incorporation applied to radiopharmaceutical kit formulation when considering clinical applications of radiopharmaceuticals. However, the increasing availability and use of PET radiopharmaceutical agents and the availability of multi modality imaging such as PET/CT will ensure the continued radiopharmaceutical development of short-lived, positron emitting diagnostic agents. Generator systems may offer a solution to centers where there is no readily available source of short-lived PET radioisotopes and for specific applications including radiotherapy. A list of several accelerator produced generator systems which are currently in use and may become more widely used in the future is given in Table 1.

TABLE 1. EXAMPLES OF GENERATORS YIELDING POSITRON EMITTING DAUGHTER RADIONUCLIDES OF CLINICAL INTEREST

| Parent (Half Life) | Decay Mode (%) | Daughter (Half-Life) | Decay Mode (%) | Characteristic $\gamma$-Energy(%) |
|---|---|---|---|---|
| Sr-82<br>(25 days) | EC(100) | Rb-82<br>(76 seconds) | $B^+$(96),EC(4) | 0.78 MeV (13.5) |
| Ge-68<br>(275 days) | EC(100) | Ga-68<br>(68 minutes) | $B^+$(88),EC(12) | 1.078 MeV<br>(3.5) |
| Zn-62<br>(9.13 hours) | $B^+$(18),EC(82) | Cu-62<br>(9.8 minutes) | $B^+$(98) | 1.17 MeV<br>(0.5) |
| Xe-122<br>(20.1 hours) | EC(100) | I-122<br>(3.6 minutes) | $B^+$(77),EC(23) | 0.56 MeV<br>(18.4) |
| Ac-225<br>(10 days) | alpha (100) | Bi-213<br>(45.6 min) | beta (98)<br>alpha (2) | 0.440 MeV<br>(28.0) |
| Rn-211<br>(14.7 hrs) | EC (74)<br>alpha (26) | At-211<br>(7.2 hrs) | alpha (42)<br>EC (58) | 0.079 MeV<br>(21.3) |

In the future, these and other radioisotope generators may become a significant fraction of clinical PET studies and of therapeutic applications.

## 8.5 HUMAN RESOURCES AND TRAINING

The efficient utilization of an accelerator facility for manufacturing radioisotopes and radiopharmaceuticals requires availability of people with variety of qualifications. These qualifications include not only the formal education in a subject appropriate for the job, but also practical training directly related to the job.

The rapid growth in this field has resulted in a critical shortage of trained personnel at all levels for the safe and appropriate handling of radioactivity including a generation gap in leadership. Most University based programs in Nuclear and Radiochemistry around the world have been phased out. Thus, in most instances, facilities must resort to on-the-job training. Such training should be structured for maximum benefit to both the trainee as well as the employer. This training must include experience in quality assurance and quality control. Furthermore, an accelerator facility should ensure that the personnel receive continuing education to maintain and improve skills and the knowledge as the new technology becomes available.

The IAEA has a long track record in fostering training in the production, handling and use of radionuclides. The present publication will be used for this purpose either as a stand alone document or in conjunction with a program that involves scientists coming together to perform collaborative research. It may also be used in advancing a participant’s ability to become more involved in independent research in the production and use of radioisotopes.

There will, however, continue to be a need for manuals for specific areas related to many of the topics discussed. While this manual is self contained, many of the topics assume a certain level of experience in the radioisotope production field.

Areas not fully covered in this document that might be considered for further development, include the processes whereby the radioisotope is converted into a more useful form, such as a radiotracer or radiopharmaceutical. In addition, while the production of generator radioisotopes has been discussed, their implementation into useful devices for biomedical research or clinical diagnostic utility has not. This area will surely be an important one to pursue, especially for regions not having direct access to an accelerator.

And finally, while this document has tried to be as comprehensive as reasonably possible, keeping in mind the constraints of page limitations, any scientific endeavour is organic and will continue to evolve, making updates and revisions necessary over time.

## 8.6 GROWTH AND TRENDS

About 350 or so cyclotrons in the world today are involved in some aspect of radionuclide production. There has been approximately an 8 % increase in the number of cyclotrons in operation since 2002. The increase has been in developed countries, but even more so in the developing countries. The largest number of cyclotrons for a single country is in the United States of America. However, taken collectively, there are more cyclotrons that are used for medical radionuclide production located in the European Union.

The number of institutions which distribute some radiopharmaceuticals and $^{18}$F-FDG, in particular, is significant and growing. In a sample of 261 centers taken by the IAEA, 75% of the cyclotrons are being used to produce FDG either for in-house use or for distribution. This is certainly an underestimate as the commercial suppliers were under represented in the survey.

The expansion in the number of cyclotrons during the last 10 years has been driven by the advent of advances in medical imaging instrumentation (PET, SPECT and more recently PET/CT), introduction of user friendly compact medical cyclotrons from several companies, and recent decisions that studies involving some PET radiopharmaceuticals are eligible for reimbursement by government or insurance companies.

There is no doubt that the fastest growing segment of the market is in the commercial distribution of $^{18}$F-FDG to local hospitals. Many centers have begun distributing FDG and at present at least 36% of the centers producing FDG are distributing it. Again this is a lower limit rather than an accurate assessment.

Over the past few decades, PET studies with radiolabeled drugs have provided new information on drug uptake, distribution, and the kinetic relationships. The increasing amount of clinically relevant information being obtained with PET has generated a demand for new routes for the widespread and cost-effective generation of the biologic radionuclides and their incorporation into appropriate radiopharmaceuticals.

The trend in the future will most likely follow two complementary directions: From one side the further growth of the number of radiopharmaceutical production centers and more widespread distribution of valuable clinical radiopharmaceuticals such as FDG, and an increasing utilization of PET/CT as the imaging modality is to be expected. The value of this combination cannot be emphasized enough.

On the other side, a number of radionuclides with nuclear properties satisfying the requirements for application in nuclear medicine are known; however, they are not yet commonly used. The diversity of physical, chemical and biochemical properties of these radionuclides justifies further exploration into this area in order to take advantage of the opportunities offered by such radionuclides. Certain applications, particularly in oncology, require tracer kinetics to be followed for periods exceeding the limits of conventional short-lived PET radionuclides. This is often necessary for pharmacokinetic studies of radiolabeled anti-cancer drugs and other molecules such as monoclonal antibodies, where tissue uptake kinetics far exceeds the limits of short-lived PET radionuclides.

The medium half-life PET radiotracers could find application in micro-dosimetry of therapeutic procedures based on radionuclides. Many of the therapeutic radionuclides are not convenient for SPECT or PET imaging; therefore their *in vivo* biodistribution in patients, and consequently the patient specific microdosimetry, cannot be traced during the treatment procedure. The simultaneous administration of the same radiopharmaceutical labeled with a therapeutic radionuclide and its positron-emitting analogue will enable the determination of the biodistribution of the therapeutic radionuclide in every patient, and the calculation of the dose delivered to the tumor and critical organs.

The high linear energy transfer (LET) and short range of α-particles allow for very high potency and specificity in α-endoradiotherapy. The spectrum of malignant diseases that may be treated with α-emitters includes most common cancers when single cells in circulation or small clusters of cells are the potential target.

With the increasing number of operational radiopharmaceutical production centers the potential for the required R&D needed for the development of production technologies of these novel radionuclides and the corresponding labeling procedures is also growing. Thus, it is to be expected that the number of clinical applications of novel radionuclides and radiopharmaceuticals will dramatically increase in the near future.

# APPENDIX 1: PET CYCLOTRON COMPARISON

| **Feature** | **PETrace** | **MiniTrace** | **RDS-111** | **Cyclone 10/5** | **Cyclone 18/9** | **TR-13** | **TR-19/9** | **HM-18** | **HM-12** |
|---|---|---|---|---|---|---|---|---|---|
| Manufacturer | GE Medical Systems | GE Medical Systems | CTI | Ion Beam Applications | Ion Beam Applications | Advanced Cyclotron Systems | Advanced Cyclotron Systems | Sumitomo Heavy Industries Ltd | Sumitomo Heavy Industries Ltd |
| Headquarters location | New York, USA | New York, USA | Tennessee, USA | Brussels, BELGIUM | Brussels, BELGIUM | Vancouver, CANADA | Vancouver, CANADA | Tokyo JAPAN | Tokyo JAPAN |
| Years in Operation | 8 (21) | 8 (21) | ~ 15 | 11 | 11 | 7 | 7 | 15 | 15 |
| Origin of TechNology | Scanditronix (MC-17) | PETrace | Berkeley (TCC) | CRC (Louvain) | CRC (Louvain) | TRIUMF (Vancouver) | TRIUMF (Vancouver) | Sumitomo | Sumitomo |
| Factory location | Uppsala, SWEDEN | Uppsala, SWEDEN | Knoxville, TN, USA | LLN, BELGIUM | LLN, BELGIUM | Vancouver, CANADA | Vancouver, CANADA | Niihama JAPAN | Niihama JAPAN |
| Production | Internal | Internal | Internal | Internal | Internal | Internal | Internal | Internal | Internal; |
| QA Standard | ISO 9001 | ISO 9001 | ISO 9001 | ISO + EN | ISO + EN | ISO 9002 | ISO 9002 | ISO9001 | ISO9001 |
| Installed Base as of 2005 | >40 | >10 | >50 | >22 | >55 | 2 | 8 | 32 | 29 |
| % Sites that meet spec | 100% | 100% | 100 % | 100 % | 100 % | 100 % | 100 % | 100% | 100% |

| Feature | PETrace | MiniTrace | RDS-111 | Cyclone 10/5 | Cyclone 18/9 | TR-13 | TR-19/9 | HM-18 | HM-12 |
|---|---|---|---|---|---|---|---|---|---|
| **Beam** | | | | | | | | | |
| Proton | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Deuteron | Yes | No | No | Yes | Yes | No | Yes | Yes | Yes |
| Proton MeV | 16.5 | 9.6 | 11 | 10 | 18 | 14 | 19.0 | 18 | 12 |
| Deut. MeV | 8.6 | - | No | 5.0 | 9.0 | No | 9.0 | 10 | 6 |
| Variable Energy Extr. | No | No | No | No | No | Yes, 11 to 14 | Yes, 14 to 19.0 | No | No |
| Variable Current Extr. | Yes | Yes | Yes | Yes | Yes | Yes, from 1:1 to 1: 100 | Yes, from 1:1 to 1:100 | Yes | Yes |
| Extracted Proton (µA) | 80 | 50 | 60 | 80 | >100 | > 100 | > 150 | > 100<br>> 150 (option) | > 100<br>> 150 (option) |
| Extracted Deut. (µA) | 60 | - | No | 40 | 40 | No | > 75 | 40 | 40 |
| **Targets** | | | | | | | | | |
| No. of Targets | 6 (2 x 3) | 6 (1+5) | 14 (2 x 7) | 8 | 8 | 8 (2 x 4) | 8 (2 x 4) | 8 (2 x 4) | 8 (2 x 4) |
| Position of targets | together on one side of cyclotron | | dual ports | evenly spaced inside magnet yoke | evenly spaced inside magnet yoke | 2 ports<br>4 targets | 2 ports<br>4 targets | 2 ports<br>4 targets | 2 ports<br>4 targets |
| Dual simult. Irradiation | Yes, targets must be 3 positions apart | Yes | Yes (right and left side) | Yes, on opposite targets | Yes, on opposite targets | Yes (right and left side) | Yes (right and left side) | Yes | Yes |
| stable beam dual irradiation | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| No. target comb. dual irr. | 6 | 5 | > 20 | 4 | 4 | 16 | 16 | 16 | 16 |
| can steer target to beam. | Can optimize beam on tgt by moving beam. | Can optimize beam on tgt by moving beam. | No | Optimize beam by moving stripper foil position | Optimize beam by moving stripper foil position | Yes | Yes | Yes | Yes |
| complexity of target system | Low | Low | high | Low | Low | Medium | Medium | Low | Low |
| Open Tank to service target | No | No | No | Yes | No | No | No | No | No |
| Time to service targets | ~ 1 minute | ~3 minutes | ~ 10 minutes | ~ 10 minutes | ~ 5 minutes | ~ 10 minutes | ~ 10 minutes | ~ 10 minutes | ~ 10 minutes |

| **Feature** | **PETrace** | **MiniTrace** | **RDS-111** | **Cyclone 10/5** | **Cyclone 18/9** | **TR-13** | **TR-19/9** | **HM-18** | **HM-12** |
|---|---|---|---|---|---|---|---|---|---|
| **Ion Source** | | | | | | | | | |
| I.S. Type | Internal | Internal | Internal | Internal | Internal | External | External | Internal | Internal |
| Source Type | Cold Cathode, Penning I.G. | Cold Cathode Penning I.G | Cold Cathode, Penning I.G. | Cold Cathode, Penning I.G. | Cold Cathode, Penning I.G. | Filament, microcusp | Filament, microcusp | Cold cathode PIG | Cold cathode PIG |
| I.S. TechNology | Scanditronix 1965 | Scanditronix 1965 | Berkeley 1960 | New design | New design | TRIUMF, 1985 | TRIUMF, 1985 | Sumitomo | Sumitomo |
| Open tank to service I.S. | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| Down time to service I.S. | < 1 hour | < 1 hour | > 1 hour | < 1 hour | < 1 hour | ~ 10 minutes | ~ 10 minutes | < 1 hour | <1 hour |
| Gas load to vacuum tank | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| | | | | | | | | | |
| **Vacuum Sys.** | | | | | | | | | |
| Vacuum Pumps | 1 mech.,<br>1 oil diff<br>2600 lps | 1 mech.,<br>1 oil diff<br>2600 lps | 1 mech.,<br>1 oil diff<br>2000 lps | 1 mech.,<br>1 oil diffusion | 1 mech.,<br>4 oil diffusion | 1 turbo ,<br>2 cryopumps | 1 turbo,<br>2 cryopumps | 1 mech.,<br>2 oil diff<br>6000 lps | 1 mech.,<br>2 oil diff<br>6000 lps |
| Oil in Vacuum tank | limited amount | limited amount | Yes | Yes | Yes | No | No | limited amount | limited amount |
| Op. Vacuum | 5 x $10^{-6}$ | 5 x $10^{-6}$ | 3 x $10^{-6}$ | 3 x $10^{-6}$ | 3 x $10^{-6}$ | 2 x $10^{-7}$ | 2 x $10^{-7}$ | 1 x $10^{-5}$Pa | 1 x $10^{-5}$Pa |
| I.S. Lock | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Target Lock | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Clean Vac. | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |

| **Main Magnet** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pole Diameter | 0.83 m | 0.7 m | 0.9 m | 0.76 | 1.08 m | | | 1.08 m | 0.8 m |
| Extraction Radius | 0.42 m | 0.34 m | 0.4 m | 0.35 | 0.48 | | | 0.46m | 0.33m |
| No. of sectors | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Symmetric | No | | No | No | No | Yes | Yes | No | No |
| Shimming | No | No | edges ground | edges ground | edges ground | shim pieces | shim pieces | No | No |
| Hill Field | 1.9 T | 2.2 T | 1.9 | 1.9T | 1.9 T | 1.9 T | 1.9 T | 2.0 T | 2.0 T |
| Valley Field | 1.7 T | 0.9 T | 0.35 T | 0.4 T | 0.35 T | 0.55 T | 0.55 T | 0.5 T | 0.4 T |
| Mean Field | 1.8 T | 1.66 T | 1.2 T | 1.35 T | 1.3 T | 1.2 T | 1.2 T | 1.46 T | 1.5 T |
| Hill / Valley | ~ 1 | ~ 2 | ~ 5 | ~ 5 | ~ 5 | ~ 3 | ~ 3 | ~ 4 | ~ 5 |
| Iron Sat@ ctr | No | No | Yes | No | No | No | No | No | No |
| Ampere Turn | > 80 000 /coil | 75 000/coil | 51 000 | 112 000 | 112 000 | 84 000 | 84 000 | 97200 | 100000 |
| Power (kW) | 20 | 10.8 | 16 | 17 | 15 | 22 | 28 | 24 | 16 |
| Weight (kg) | 19 600 | 10 000 | 13 500 | 13 500 | 22 000 | 22 000 | 22 000 | | |
| Coil type | holLow core, copper | holLow core, copper | strip wound, copper | strip wound, copper | strip wound, copper | holLow core, copper | holLow core, copper | holLow core, copper | holLow core, copper |
| heat transfer | direct cooling | direct cooling | conduction | conduction | direct cooling | direct cooling | direct cooling | direct cooling | direct cooling |

| **Feature** | **PETrace** | **MiniTrace** | **RDS-111** | **Cyclone 10/5** | **Cyclone 18/9** | **TR-13** | **TR-19/9** | **HM-18** | **HM-12** |
|---|---|---|---|---|---|---|---|---|---|
| **RF System** | | | | | | | | | |
| Number of Dees | 2 | 2 | 4 | 2 | 2 | 2 | 2 | 2 | 2 |
| Dee Angle (degrees) | 75 | 34 | 30 | 30 | 30 | 45 | 45 | 45 | 45 |
| Harmonic Mode proton | first | fourth | fourth | second | second | fourth | fourth | second | second |
| Frequency MHz (proton) | 27.2 | 101 | 72 | 40 | 42 | 73 | 73 | 45 | 45 |
| Harmonic Mode Deut | first | n/a | n/a | fourth | fourth | n/a | fourth | fourth | fourth |
| Frequency MHz (Deut.) | 27.8 | n/a | n/a | 42 | 42 | n/a | 37 | 45 | 45 |
| Dee Volt. kV | 35 | 35 | 30 | 32 | 32 | 50 | 50 | 30 | 30 |
| RF Pwr kW | 13 | 9 | 5 | 9 | 7 | ~ 10 | ~ 10 | 15 | 15 |
| RF Stability | good | good | good | good | good | good | good | good | good |
| Solid Dees | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Dee Cooling | direct cooling | direct cooling | conduction | conduction | conduction | direct cooling | direct cooling | direct cooling | direct cooling |
| RF Coupling | inductive, by coaxial cable | inductive, by coaxial cable | inductive, by coaxial cable | inductive, by coaxial cable | inductive, by coaxial cable | capacitive, 50 mm copper trans. line | capacitive, 50 mm copper trans. line | capacitive, direct | inductive, direct |
| RF Matching | Fixed (by coaxial cable) | Fixed (by coaxial cable) | Fixed (by coaxial cable) | Fixed (by coaxial cable) | Fixed (by coaxial cable) | Computer controlled | Computer controlled | Fixed | Fixed |
| RF Matching | | | | Computer Controlled | Computer Controlled | | | | |
| Driving Sys. | Crystal | Crystal | Crystal | Synthesizer | Synthesizer | Synthesizer | Synthesizer | Crystal | Crystal |
| Amplifier Location | Away from cyclotron, No Rad. Haz | Away from cyclotron, No Rad. Haz | On cyclotron, prone to Rad. damage | Away from cyclotron, No Rad. Haz | Away from cyclotron, No Rad. Haz | away from cyclotron, No Rad. Haz. | away from cyclotron, No Rad. Haz. | On cyclotron | Away from cyclotron |
| RF Technology | Scanditronix 1990 | GE 1995 | Berkeley (TCC) 1960 | IBA | IBA | TRIUMF, 1985 | TRIUMF, 1985 | Sumitomo | Sumitomo |

| Feature | PETrace | MiniTrace | RDS-111 | Cyclone 10 | Cyclone 18/9 | TR-13 | TR-19/9 | HM-18 | HM-12 |
|---|---|---|---|---|---|---|---|---|---|
| **Yields** | | | | | | | | | |
| Carbon -11 ($CO_2$) | 30 Min., 3000 mCi | 30 min. 900 mCi | 40 min, 1000 mCi | 30 min, 1000 mCi | 30 min., 3000 mCi | 40 min., 1000 mCi | 30 min., 3000 mCi. | 40 min. 2800 mCi | 40 min. 2600 mCi |
| Nitrogen-13 ($NH_3$) | 30 min., 450 mCi | 30 min 75 mCi | 10min., 100 mCi | 15min., 150 mCi | 15 min., 400 mCi | 10 min., 150 mCi | 10 min., 600 mCi | 30min 240 mCi | 30min 125 mCi |
| Oxygen-15 ($O_2$) | 6 min., 2000 mCi | 10 min 1000 mCi | 2 min., 1000 mCi | 2 min., 500 mCi | 2 min., 1000 mCi | 2 min., 1000 mCi | 2 min., 2000 mCi | Continuous 360 mCi | Continuous 100 mCi |
| Fluorine-18 ($F^-$) | 60 min., 2500 mCi | 60 min 1000 mCi | 60 min., 1200 mCi | 60 min., 800 mCi | 60 min., 1700 mCi | 60 min., 1200 mCi | 60 min., > 2000 mCi | 60 min. 4500 mCi | 60 min. 3100 mCi |
| F-18 Target type | Silver | Silver | Silver | Niobium | Niobium | Titanium | Titanium | Niobium | Niobium |
| Max. beam on F-18 tgt. | >50 µA | > 35 µA | ~ 30 µA | ~ 50 µA | ~80 µA | ~ 40 µA | ~ 50 µA | ~65 µA | ~ 80 µA |
| Decay corr. Yld of FDG | >55 % | 55 % | 50 % | 55 % | 55 % | 65 % | 65 % | 60% | 60% |
| EOS FDG yld | 1100 mCi (45%) | 450 mCi (45%) | 360 mCi | 150 mCi | 230 mCi | 450 mCi | > 750 mCi | 2700 mCi | 1860 mCi |
| **Site Requirement** | | | | | | | | | |
| Dee Orientation | Vertical | Vertical | Horizontal | Horizontal | Horizontal | Vertical | Vertical | Horizontal | Vertical |
| Weight w/o shield (kg) | 18.000 | 9.100 | 10.000 | 12.000 | 21.000 | 20.000 | 20.000 | 24.000 | 11.000 |
| Self-Shield option available | Yes | Yes integrated | Yes | Yes, but vault recommended | Yes, but vault recommended | Yes | Yes | Yes | Yes |
| Self- shield material | boronated water | composite | composite | composite | composite | composite | composite | composite | composite |
| wt. of self-shield (kg) | 45.000 | 36.000 | 27.000 | ~45.000 | 73.000 | 54.000 | 54.000 | 86.000 | 56.000 |
| Rad. Fld at 1 meter | ~ 10 µSv /hr | 10 µSv / hr | ~ 40 µSv /hr | ~ 10 µSv /hr | ~ 10 µSv /hr | ~ 20 µSv /hr | ~ 20 µSv /hr | ~ 50 µSv /hr | ~ 50 µSv /hr |
| Pwr Requ. | 66 kW @ 208-480 V | 35 kW @ 208-480 V | 35 kW @ 208-480 V | 35 kW @ 208-480 V | 60 kW @ 208-480 V | 60 kW @ 208-480 V | 65 kW @ 208-480 V | 55kW@ 200V | 45kW@ 200V |
| Acceleration Plane | Vertical | Vertical | Horizontal | Horizontal | Horizontal | Vertical | Vertical | Horizontal | Vertical |

| **Feature** | **PETrace** | **MiniTrace** | **RDS-111** | **Cyclone 10** | **Cyclone 18/9** | **TR-13** | **TR-19/9** | **HM-18** | **HM-12** |
|---|---|---|---|---|---|---|---|---|---|
| Computer Control Syst. | SUN SPARC 20 | SUN SPARC 20 | PC | PC/Win NT | PC/Win NT | PC | PC | PC | PC |
| Computer Platform | UNIX | UNIX | Siemens | Siemens PLC | Siemens PLC | MS-DOS | MS-DOS | Windows-XP | Windows-XP |
| Serviceability | Excellent | Excellent | Poor | Excellent | Excellent | Medium | Medium | Excellent | Excellent |
| Fault Diagnostics | Extensive | Extensive | Limited | Extensive | Extensive | Extensive | Extensive | Extensive | Extensive |
| Software | .Strong | Strong | Strong | Strong | Strong | Strong | Strong | Strong | Strong |

# APPENDIX 2: HIGH ENERGY CYCLOTRON COMPARISON

| **Feature** | **Cyclone 30** | **Cyclone 70** | **TR30** |
|---|---|---|---|
| Manufacturer | IBA | IBA | ACS |
| Headquarters location | Louvain la Neuve, Belgium | Louvain la Neuve, Belgium | Richmond Canada |
| Origin of Technology | University of Louvain | IBA | TRIUMF 1985 |
| Factory location | Louvain la Neuve, Belgium | Louvain la Neuve, Belgium | Richmond Canada |
| Production | Louvain la Neuve, Belgium | Louvain la Neuve, Belgium | |
| QA Standard | ISO 9001 | ISO 9001 | ISO manufacturing |
| Installed Base | 21 | | 4 |
| % Sites that meet spec | 100 | | 100 |
| **Beam** | | | |
| Proton | 400- 750 -1200 µA model | Proton 70 MeV | >1000 uA |
| Deuteron | option | Yes | 100 uA |
| Proton MeV | 15- 30 MeV | 25- 70 MeV | 15-30 |
| Deut. MeV | 9-15 MeV | 15- 35 MeV | 7.5-15 |
| Variable Energy Extraction | Yes | Yes | 15-30 MeV |
| Variable Current Extraction | Yes | Yes | split ratio 1:100 |
| **Extracted Proton ( A)** | 400- 750 -1200 µA model | 350 - 750 µA proton | >1000uA |
| **Extracted Deut. ( A)** | option | Yes | 100 uA |

| **Feature** | **Cyclone 30** | **Cyclone 70** | **TR30** |
|---|---|---|---|
| **Targets** | | | |
| No. of Targets | up to 10 per cyclotron | | up to 10 per cyclotron |
| | up to 6 beam lines | up to 6 beam lines | up to 6 beam lines |
| Position of targets | in target bunker | in target bunker | at end of beam line. |
| | SPECT target | SPECT target | |
| | 250 - 600 µA | 250 - 600 µA | |
| | Gas target | Gas target | |
| | 100 µA | 100 µA | |
| Dual simult. Irradiation | Yes, standard | Yes, standard | Yes |
| stable beam dual irradiation. | Yes, regulated | Yes, regulated | Yes |
| Target selector | switching magnet | switching magnet | switching magnet |
| No. target comb. dual irrad. | 2 | 2 | 2 |
| can steer target. to beam. | Yes | Yes | Yes |
| complexity of target system | low | low | complex |
| Open Tank to service target | No | No | No |
| Time to service targets | reduced | reduced | automatic insertions and retraction. |
| | | | All external target stations |
| **Vacuum System** | | | |
| Vacuum Pumps | Cryo pump | Cryo pump | 2 Cryopumps |
| Oil in Vacuum tank | No | No | No |
| Op. Vacuum | 10-7 torr | 10-7 torr | 2 x 10-7 torr |
| I.S. Lock | Yes | Yes | Yes |
| Target Lock | Yes | Yes | targets on separate beam line |
| Clean Vacuum | Yes | Yes | Yes |

| **Feature** | **Cyclone 30** | **Cyclone 70** | **TR30** |
|---|---|---|---|
| **Main Magnet** | | | |
| Pole Diameter | 1.6 m | | 1.5 m |
| Extraction Radius | 0.5- 0.75 | | 0.66 m |
| No. of sectors | 4 | 4 | 4 |
| Symmetric | Yes | Yes | Yes |
| Shimming | edges ground | edges ground | shim pieces |
| Hill Field | 1.7 T | 1.7 T | 1.9 T |
| Valley Field | 0.12 T | 0.12 T | 0.5 T |
| Mean Field | 1 T | 1 T | 1.2 T |
| Hill / Valley | 14 | 14 | 3.8 |
| Iron Sat@ center | No | | No |
| Ampere Turn | 60 000 | | 7.2 x 10**4 |
| Power (kW) | 7,2 | 60 | 32 |
| Weight (kg) | 50 000 | 135 000 | 50 000 |
| Coil type | hollow copper core | hollow copper core | hollow core copper |
| heat transfer | direct cooling | direct cooling | direct cooling |

| **Feature** | **Cyclone 30** | **Cyclone 70** | **TR30** |
|---|---|---|---|
| **RF System** | | | |
| Number of Dees | 2 | 2 | 4 |
| Dee Angle (degrees) | 30 | 30 | 45 |
| Harmonic Mode proton | 4th | 2nd | 4th |
| Frequency MHz (proton) | 66 | 30 | 73 |
| Harmonic Mode Deut. | option | 4 | 4 |
| Frequency MHz (Deuteron) | option | 30 | |
| Dee Volt. kV | 50 | 50 | 50 |
| RF Power kW | 40 -100 kW max. | 100 kW | 40-100 |
| RF Stability | excellent | excellent | excellent |
| Solid Dees | Yes | Yes | Yes |
| Dee Cooling | conduction | conduction | direct cooling |
| RF Coupling | direct resonant | inductive | Capacitive |
| trans. line | No | Yes short | 150-200 mm Copper |
| RF Matching | variable capacitor | variable capacitor | computer controlled |
| Driving Sys. | PLL synthesizer | PLL synthesizer | synthesizer |
| Amplifier Location | coupled to cyclotron | inductive coupling on stem | away from cyclotron, No Rad. Haz. |
| RF TechNology | IBA, resonant cavity design | IBA, resonant cavity design | TRIUMF 1985 |

| **Feature** | **Cyclone 30** | **Cyclone 70** | **TR30** |
|---|---|---|---|
| **Site Requireuirement** | | | |
| Dee | | | n/a |
| Orientation | horizontal | horizontal | horiz. Median plane |
| Rad. Fld | bunker shield | bunker shield | n/a |
| Pwr Requ. | 150 KVA | 250 KVA | 80 kW |
| Acceleration Plane | Horizontal | Horizontal | horizontal |
| Computer Control Syst. | Siemens PLC | Siemens PLC | |
| Computer Platform | Windows NT | Windows NT | PC &Allen Bradley PLC |
| Serviceability | Good | Good | Good |
| Fault DiagNostics | Excellent | Excellent | Extensive |
| Software | Strong | Strong | MS-XP and AB PLC programming |

# ANNEXES IN CD FORM

**ANNEX 1: Detailed Calculation of Beam Heating Effects on Thallium Target**

**ANNEX 2: Optimisation of Production Yields, Radionuclidic Purity and Hotcell Shielding of the $^{67}$Ga Spect Radionuclide Produced by Proton Irradiation in 30 MeV Cyclotrons**

**ANNEX 3: Excel Work Sheet for Calcualtion of Production Yields for $^{67}$Ga, $^{111}$In, $^{201}$Pb ($^{201}$Tl) and $^{18}$F Radionuclides by (p,xn) reactions, Dose Rates and Lead Shielding of Hotcells**

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