

Production of Long Lived Parent Radionuclides for Generators: ^{68}Ge , ^{82}Sr , ^{90}Sr and ^{188}W



IAEA

International Atomic Energy Agency

IAEA RADIOISOTOPES AND RADIOPHARMACEUTICALS SERIES PUBLICATIONS

One of the main objectives of the IAEA Radioisotope Production and Radiation Technology programme is to enhance the expertise and capability of IAEA Member States in deploying emerging radioisotope products and generators for medical and industrial applications in order to meet national needs as well as to assimilate new developments in radiopharmaceuticals for diagnostic and therapeutic applications. This will ensure local availability of these applications within a framework of quality assurance.

Publications in the IAEA Radioisotopes and Radiopharmaceuticals Series provide information in the areas of: reactor and accelerator produced radioisotopes, generators and sealed sources development/production for medical and industrial uses; radiopharmaceutical sciences, including radiochemistry, radiotracer development, production methods and quality assurance/quality control (QA/QC). The publications have a broad readership and are aimed at meeting the needs of scientists, engineers, researchers, teachers and students, laboratory professionals, and instructors. International experts assist the IAEA Secretariat in drafting and reviewing these publications. Some of the publications in this series may also be endorsed or co-sponsored by international organizations and professional societies active in the relevant fields.

There are two categories of publications: the **IAEA Radioisotopes and Radiopharmaceuticals Series** and **IAEA Radioisotopes and Radiopharmaceuticals Reports**.

IAEA RADIOISOTOPES AND RADIOPHARMACEUTICALS SERIES

Publications in this category present guidance information or methodologies and analyses of long term validity, for example protocols, guidelines, codes, standards, quality assurance manuals, best practices and high level technological and educational material.

IAEA RADIOISOTOPES AND RADIOPHARMACEUTICALS REPORTS

In this category, publications complement information published in the IAEA Radioisotopes and Radiopharmaceuticals Series in areas of the: development and production of radioisotopes and generators for medical and industrial applications; and development, production and QA/QC of diagnostic and therapeutic radiopharmaceuticals. These publications include reports on current issues and activities such as technical meetings, the results of IAEA coordinated research projects, interim reports on IAEA projects, and educational material compiled for IAEA training courses dealing with radioisotope and radiopharmaceutical related subjects. In some cases, these reports may provide supporting material relating to publications issued in the IAEA Radioisotopes and Radiopharmaceuticals Series.

All of these publications can be downloaded cost free from the IAEA web site:

<http://www.iaea.org/Publications/index.html>

Further information is available from:

Marketing and Sales Unit
International Atomic Energy Agency
Vienna International Centre
PO Box 100
1400 Vienna, Austria

Readers are invited to provide feedback to the IAEA on these publications. Information may be provided through the IAEA web site, by mail at the address given above, or by email to:

Official.Mail@iaea.org

PRODUCTION OF LONG LIVED
PARENT RADIONUCLIDES FOR
GENERATORS: ^{68}Ge , ^{82}Sr , ^{90}Sr AND ^{188}W

The following States are Members of the International Atomic Energy Agency:

AFGHANISTAN	GHANA	NORWAY
ALBANIA	GREECE	OMAN
ALGERIA	GUATEMALA	PAKISTAN
ANGOLA	HAITI	PALAU
ARGENTINA	HOLY SEE	PANAMA
ARMENIA	HONDURAS	PARAGUAY
AUSTRALIA	HUNGARY	PERU
AUSTRIA	ICELAND	PHILIPPINES
AZERBAIJAN	INDIA	POLAND
BAHRAIN	INDONESIA	PORTUGAL
BANGLADESH	IRAN, ISLAMIC REPUBLIC OF	QATAR
BELARUS	IRAQ	REPUBLIC OF MOLDOVA
BELGIUM	IRELAND	ROMANIA
BELIZE	ISRAEL	RUSSIAN FEDERATION
BENIN	ITALY	SAUDI ARABIA
BOLIVIA	JAMAICA	SENEGAL
BOSNIA AND HERZEGOVINA	JAPAN	SERBIA
BOTSWANA	JORDAN	SEYCHELLES
BRAZIL	KAZAKHSTAN	SIERRA LEONE
BULGARIA	KENYA	SINGAPORE
BURKINA FASO	KOREA, REPUBLIC OF	SLOVAKIA
BURUNDI	KUWAIT	SLOVENIA
CAMBODIA	KYRGYZSTAN	SOUTH AFRICA
CAMEROON	LATVIA	SPAIN
CANADA	LEBANON	SRI LANKA
CENTRAL AFRICAN REPUBLIC	LESOTHO	SUDAN
CHAD	LIBERIA	SWEDEN
CHILE	LIBYAN ARAB JAMAHIRIYA	SWITZERLAND
CHINA	LIECHTENSTEIN	SYRIAN ARAB REPUBLIC
COLOMBIA	LITHUANIA	TAJIKISTAN
CONGO	LUXEMBOURG	THAILAND
COSTA RICA	MADAGASCAR	THE FORMER YUGOSLAV REPUBLIC OF MACEDONIA
CÔTE D'IVOIRE	MALAWI	TUNISIA
CROATIA	MALAYSIA	TURKEY
CUBA	MALI	UGANDA
CYPRUS	MALTA	UKRAINE
CZECH REPUBLIC	MARSHALL ISLANDS	UNITED ARAB EMIRATES
DEMOCRATIC REPUBLIC OF THE CONGO	MAURITANIA	UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND
DENMARK	MAURITIUS	UNITED REPUBLIC OF TANZANIA
DOMINICAN REPUBLIC	MEXICO	UNITED STATES OF AMERICA
ECUADOR	MONACO	URUGUAY
EGYPT	MONGOLIA	UZBEKISTAN
EL SALVADOR	MONTENEGRO	VENEZUELA
ERITREA	MOROCCO	VIETNAM
ESTONIA	MOZAMBIQUE	YEMEN
ETHIOPIA	MYANMAR	ZAMBIA
FINLAND	NAMIBIA	ZIMBABWE
FRANCE	NEPAL	
GABON	NETHERLANDS	
GEORGIA	NEW ZEALAND	
GERMANY	NICARAGUA	
	NIGER	
	NIGERIA	

The Agency's Statute was approved on 23 October 1956 by the Conference on the Statute of the IAEA held at United Nations Headquarters, New York; it entered into force on 29 July 1957. The Headquarters of the Agency are situated in Vienna. Its principal objective is "to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world".

IAEA RADIOISOTOPES AND RADIOPHARMACEUTICALS SERIES No. 2

PRODUCTION OF LONG LIVED
PARENT RADIONUCLIDES FOR
GENERATORS: ^{68}Ge , ^{82}Sr , ^{90}Sr AND ^{188}W

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2010

COPYRIGHT NOTICE

All IAEA scientific and technical publications are protected by the terms of the Universal Copyright Convention as adopted in 1952 (Berne) and as revised in 1972 (Paris). The copyright has since been extended by the World Intellectual Property Organization (Geneva) to include electronic and virtual intellectual property. Permission to use whole or parts of texts contained in IAEA publications in printed or electronic form must be obtained and is usually subject to royalty agreements. Proposals for non-commercial reproductions and translations are welcomed and considered on a case-by-case basis. Enquiries should be addressed to the IAEA Publishing Section at:

Marketing and Sales Unit, Publishing Section
International Atomic Energy Agency
Vienna International Centre
PO Box 100
1400 Vienna, Austria
fax: +43 1 2600 29302
tel.: +43 1 2600 22417
email: sales.publications@iaea.org
<http://www.iaea.org/books>

© IAEA, 2010

Printed by the IAEA in Austria
May 2010
STI/PUB/1436

IAEA Library Cataloguing in Publication Data

Production of long lived parent radionuclides for generators : ^{68}Ge , ^{82}Sr , ^{90}Sr and ^{188}W . — Vienna : International Atomic Energy Agency, 2010.
p. ; 24 cm. — (IAEA radioisotopes and radiopharmaceuticals series, ISSN 2077-6462 ; no. 2)
STI/PUB/1436
ISBN 978-92-0-101110-7
Includes bibliographical references.

1. Radionuclide generators. 2. Radioisotopes. 3. Nuclear medicine.
I. International Atomic Energy Agency. II. Series.

IAEAL

10-00628

FOREWORD

Radionuclide generators represent convenient in-house radionuclide production systems that allow daughter species to be obtained even in the absence of on-site reactor or accelerator facilities. The resurgence in interest in the use of radionuclide generator systems is due to the development of new targeting strategies using specific carrier molecules for the development of both diagnostic and therapeutic radiopharmaceuticals.

This publication provides information on the production and processing of four important long lived parent radionuclides, ^{68}Ge , ^{82}Sr , ^{90}Sr and ^{188}W , used for the preparation of generators for nuclear medicine applications such as positron emission tomography (PET) or therapy. Germanium-68 is used for the $^{68}\text{Ge}/^{68}\text{Ga}$ generator system, which provides no-carrier-added ^{68}Ga for use in PET imaging. Gallium-68 labelled tumour specific peptides are now in routine use for PET imaging of certain types of cancer. Strontium-82 is used as the parent for the production of $^{82}\text{Sr}/^{82}\text{Rb}$ generator systems. Rubidium-82 is an important PET marker for myocardial perfusion studies. This report describes the processing and purification of ^{90}Sr from fission products, which can provide ^{90}Sr suitable for fabrication of the $^{90}\text{Sr}/^{90}\text{Y}$ generator. Yttrium-90 is widely used for a variety of important therapeutic applications. Reactor production and subsequent processing of ^{188}W provides this important parent species for fabrication of the $^{188}\text{W}/^{188}\text{Re}$ generator system to obtain ^{188}Re perrhenate for incorporation into various therapeutic agents.

The IAEA thanks all the consultants who contributed to this publication, as well as the reviewers. F.F. Knapp, Jr., of the Oak Ridge National Laboratory, USA, provided valuable help in editing the manuscript. The IAEA officer responsible for this publication was M.R.A. Pillai of the Division of Physical and Chemical Sciences.

EDITORIAL NOTE

The use of particular designations of countries or territories does not imply any judgments by the publisher, the IAEA, as to the legal status of such countries or territories, of their authorities and institutions or of the delimitation of their boundaries.

The mention of names of specific companies or products (whether or not indicated as registered) does not imply any intention to infringe proprietary rights, nor should it be construed as an endorsement or recommendation on the part of the IAEA.

The authors are responsible for having obtained the necessary permission for the IAEA to reproduce, translate or use material from sources already protected by copyrights.

CONTENTS

CHAPTER 1. INTRODUCTION	1
1.1. Background	1
1.2. Objective	7
1.3. Scope	8
1.4. Structure	8
References to Chapter 1	8
CHAPTER 2. PRODUCTION, RADIOCHEMICAL PROCESSING AND QUALITY EVALUATION OF ^{68}Ge	11
<i>F. Roesch, D.V. Filosofov</i>	
2.1. Introduction	11
2.2. Background	12
2.3. Nuclear decay characteristics	15
2.4. ^{68}Ge production	15
2.5. Chemical aspects	24
2.6. Conclusion	27
References to Chapter 2	28
CHAPTER 3. PRODUCTION AND PROCESSING OF ^{82}Sr	31
<i>K.D. John, L. Mausner, T.J. Ruth</i>	
3.1. Introduction	31
3.2. Background	32
3.3. Nuclear decay characteristics	32
3.4. Production processes	33
3.5. Chemical aspects	39
3.6. Conclusion	42
References to Chapter 3	42
Bibliography	44
CHAPTER 4. RECOVERY, PURIFICATION AND QUALITY EVALUATION OF ^{90}Sr	49
<i>S.K. Samanta</i>	
4.1. Introduction	49
4.2. Background	50

4.3. Nuclear decay characteristics	54
4.4. Processes for the recovery of ⁹⁰ Sr from radioactive waste	55
4.5. Purification	69
4.6. Methods for evaluation of the quality of ⁹⁰ Sr	71
4.7. Conclusion	73
Acknowledgements	75
References to Chapter 4	75
CHAPTER 5. REACTOR PRODUCTION AND PROCESSING OF ¹⁸⁸ W	79
<i>F.F. Knapp, Jr., S. Mirzadeh, M. Garland, B. Ponsard, R. Kuznetsov</i>	
5.1. Introduction	79
5.2. Background	80
5.3. Nuclear decay	81
5.4. Production and processing	81
5.5. Chemical aspects	87
5.6. Processing of ¹⁸⁸ W	89
5.7. Radiological controls and radiation protection	98
5.8. Conclusion	105
Acknowledgements	106
References to Chapter 5	106
CONTRIBUTORS TO DRAFTING AND REVIEW	111

Chapter 1

INTRODUCTION

1.1. BACKGROUND

1.1.1. Radionuclide generators

A radionuclide generator is a device for effective radiochemical separation of a daughter radionuclide formed by the decay of a parent radionuclide. The goal is to obtain the daughter in a form having high radionuclidic and radiochemical purity. Essentially, every conceivable approach has been used for parent/daughter separation strategies, including solvent extraction, ion exchange, adsorption chromatography, electrochemistry and sublimation. For practical reasons, most radionuclide generator systems that are useful for medical applications involve secular equilibria, where the parent radionuclide has a half-life significantly longer than that of the daughter. This scenario permits repeated separation of the daughter from the parent.

Although many parent/daughter pairs have been evaluated as radionuclide generator systems, only a few generators are currently available and in routine clinical and research use. The most widely used radionuclide generator for clinical applications is the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator system, because of the ease of obtaining high radiochemical yields of $^{99\text{m}}\text{Tc}$, the attractive radionuclidic properties and the well established versatile chemistry for transferring the eluted $^{99\text{m}}\text{Tc}$ -pertechnetate to a broad spectrum of radiopharmaceuticals.

In the past decade, the enormous increase in the use of radionuclide generators to provide both therapeutic and positron emitting radionuclides has paralleled the complementary development of targeting agents for therapy and positron emission tomography (PET). These developments have been discussed in the literature [1.1–1.16], and detailed reviews are available addressing parent/daughter half-lives [1.17], reactor production of generator parent radionuclides [1.8], accelerator and cyclotron [1.18] production of generator parent radionuclides, ultra-short-lived generator produced radionuclides [1.19], and generator derived positron emitting radionuclides [1.12].

The development of radionuclide generators has been addressed by the IAEA through several of its coordinated research projects, and a recent publication describes the technologies developed for $^{90}\text{Sr}/^{90}\text{Y}$ and $^{188}\text{W}/^{188}\text{Re}$ generators, which are of interest in radionuclide therapy [1.20].

The availability of adequate quantities of radiochemically pure, high specific activity parent radionuclides is important in embarking upon a

programme for the production of radionuclide generators. This report describes in detail the production and processing of the parent species required for preparation of four radionuclide generator systems of current interest for both diagnostic ($^{68}\text{Ge}/^{68}\text{Ga}$ and $^{82}\text{Sr}/^{82}\text{Rb}$) and therapeutic ($^{90}\text{Sr}/^{90}\text{Y}$ and $^{188}\text{W}/^{188}\text{Re}$) applications.

1.1.2. Generator equilibrium

The generation of a daughter radionuclide formed by the decay of a parent radionuclide considers the decay parameters of the parent (denoted by subscript 1) and of the daughter (denoted by subscript 2). The decay of the parent is shown in Eq. (1.1):

$$-dN_1/dt = \lambda_1 N_1, \text{ and } N_1 = N_1^0 e^{-\lambda_1 t} \quad (1.1)$$

where λ is the decay constant for the radionuclide and N represents the number of atoms at time t . N^0 indicates the corresponding quantity when $t = 0$.

The daughter radionuclide is formed at the rate at which the parent decays, $\lambda_1 N_1$. However, the daughter itself decays at the rate $\lambda_2 N_2$, and hence the net production rate is given by:

$$dN_2/dt = \lambda_1 N_1 - \lambda_2 N_2 = \lambda_1 N_1^0 e^{-\lambda_1 t} - \lambda_2 N_2^0 e^{-\lambda_2 t} \quad (1.2)$$

Solution of this linear differential equation leads to:

$$N_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1^0 (e^{-\lambda_1 t} - e^{-\lambda_2 t}) + N_2^0 e^{-\lambda_2 t} \quad (1.3)$$

If the parent is longer lived than the daughter ($T_{1/2,1} > T_{1/2,2}$, i.e. $\lambda_1 < \lambda_2$), $e^{-\lambda_2 t}$ is negligible compared with $e^{-\lambda_1 t}$ after t becomes sufficiently large, and $N_2^0 e^{-\lambda_2 t}$ also becomes negligible. Equation (1.3) then reaches the form:

$$N_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1^0 e^{-\lambda_1 t} \quad (1.4)$$

Since $N_1 = N_1^0 e^{-\lambda_1 t}$, the ratio of the number of atoms of the two radionuclides is:

$$\frac{N_2}{N_1} = \frac{\lambda_2 - \lambda_1}{\lambda_1} \quad (1.5)$$

and, consequently, the ratio of the absolute activities, A , of the two radionuclides is:

$$\frac{A_1}{A_2} = \frac{(\lambda_2 - \lambda_1)}{\lambda_2} = 1 - \frac{\lambda_1}{\lambda_2} \quad (1.6)$$

This condition of a constant ratio of parent to daughter activity is known as radioactive equilibrium. In a limiting case, when the half-life of the parent is far longer than that of the daughter ($T_{1/2,1} \gg T_{1/2,2}$, or $\lambda_1 \ll \lambda_2$), Eqs (1.5) and (1.6) reduce to $N_1/N_2 = \lambda_2/\lambda_1$ and $A_1 = A_2$, respectively. In this type of equilibrium, the activity of the daughter is equal to the activity of the parent.

The maximum activity of the daughter occurs at time t , which is given by:

$$t = \frac{1}{\lambda_2 - \lambda_1} \ln \frac{\lambda_2}{\lambda_1} \quad (1.7)$$

A radioactive equilibrium between the parent and the daughter is referred to as a transient or secular equilibrium, depending on the relative half-lives of the parent and daughter pair. For a secular equilibrium, $T_{1/2,1} \gg T_{1/2,2}$; hence the activity of the daughter radionuclide eluted at optimum time intervals remains ‘almost’ constant for at least ten such elutions. Mathematically, this is the case if $T_{1/2,1}$ is greater than $T_{1/2,2}$ by at least an order of magnitude. For a transient equilibrium, the ratio of the half-life of the parent to that of the daughter is less than 10.

1.1.3. Generator pairs

In-house availability of daughter radionuclides is one of the key advantages of using radionuclide generator systems. Radionuclide generators can routinely provide radionuclides on demand without on-site availability of an accelerator or a research reactor. Using a generator system, it is possible to obtain a radiochemically pure daughter radionuclide by adapting a suitable and efficient separation technique. The radioisotope eluted from a generator is of the maximum achievable specific activity, as the daughter product is formed by one of the radioactive decay modes — such as positron emission, electron capture (EC), and β^- or α decay — that result in an elemental transition.

An important requirement for radionuclide generator systems for routine use is a long half-life of the parent radionuclide, to cover logistics of production and transportation. Table 1.1 lists radionuclide generator systems where the half-life of the parent radionuclide is three or more days, making them useful for life science applications.

The daughter product of a radionuclide generator will decay by any of the decay modes (isomeric transition, β^- , β^+ , electron capture, α decay) or by a

TABLE 1.1. RADIONUCLIDE GENERATOR SYSTEMS WHERE $T_{1/2,1} > 3$ d [1.16]

Generator system	Parent radionuclide			Daughter radionuclide		
	$T_{1/2}$	Main production route ^a	Main decay mode ^b	$T_{1/2}$	Main decay mode ^b	Application ^c
⁴² Ar/ ⁴² K	32.9 a	R	β^-	12.36 h	β^-	Chemistry
⁴⁴ Ti/ ⁴⁴ Sc	47.3 a	A	EC	3.93 h	β^+	PET
⁵² Fe/ ^{52m} Mn	8.28 h	A	β^+	21.1 min	β^+	PET
⁶⁸ Ge/ ⁶⁸ Ga	270.8 d	A	EC	1.14 h	β^+	PET
⁷² Se/ ⁷² As	8.4 d	A	EC	1.08 d	β^+	PET
⁸³ Rb/ ^{83m} Kr	86.2 d	A	EC	1.86 h	γ	Chemistry/RPC
⁸² Sr/ ⁸² Rb	25.6 d	A	EC	1.27 min	β^+	PET
⁹⁰ Sr/ ⁹⁰ Y	28.5 a	R, R(f)	β^-	2.67 d	β^-	ERT
⁹⁹ Mo/ ^{99m} Tc	2.75 d	R, R(f)	β^-	6.01 h	γ	SPECT
¹⁰³ Pd/ ^{103m} Rh	16.97 d	R, A	EC	56.12 min	γ , Ae	Chemistry
¹⁰⁹ Cd/ ^{109m} Ag	1.267 a	A	EC	39.6 s	γ	FPRNA
¹¹³ Sn/ ^{113m} In	115.1 d	R	EC	1.66 h	γ	Chemistry/RPC
¹¹⁸ Te/ ¹¹⁸ Sb	6.00 d	A	EC	3.6 m	β^+	PET
¹³² Te/ ¹³² I	3.26 d	R(f)	β^-	2.28 h	γ , β^-	Therapy
¹³⁷ Cs/ ^{137m} Ba	30.0 a	R, R(f)	β^-	2.55 min	γ	In vivo diagnosis
¹⁴⁰ Ba/ ¹⁴⁰ La	12.75 d	A	β^-	1.68 d	γ , β^-	Chemistry/RPC
¹³⁴ Ce/ ¹³⁴ La	3.16 d	A	EC	6.4 min	β^+	PET
¹⁴⁴ Ce/ ¹⁴⁴ Pr	284.9 d	R, R(f)	β^-	17.3 min	γ	Chemistry/RPC
¹⁴⁰ Nd/ ¹⁴⁰ Pr	3.37 d	A	EC	3.39 min	β^+ , Ae	PET
¹⁶⁶ Dy/ ¹⁶⁶ Ho	3.40 d	R	β^-	1.12 d	β^-	ERT
¹⁶⁷ Tm/ ^{167m} Er	9.24 d	A	EC	2.28 s	γ	Chemistry/RPC
¹⁷² Hf/ ¹⁷² Lu	1.87 a	A	EC	6.70 d	γ	Chemistry/RPC
¹⁷⁸ W/ ¹⁷⁸ Ta	21.5 d	A	EC	9.31 min	γ	FPRNA
¹⁸⁸ W/ ¹⁸⁸ Re	69.4 d	R	β^-	16.98 h	β^-	ERT
¹⁹¹ Os/ ^{191m} Ir	15.4 d	R	β^-	4.94 s	γ	FPRNA

TABLE 1.1. RADIONUCLIDE GENERATOR SYSTEMS WHERE $T_{1/2,1} > 3$ d [1.16] (cont.)

Generator system	Parent radionuclide			Daughter radionuclide		
	$T_{1/2}$	Main production route ^a	Main decay mode ^b	$T_{1/2}$	Main decay mode ^b	Application ^c
¹⁹⁴ Os/ ¹⁹⁴ Ir	6.0 a	R	β^-	19.15 h	γ, β^-	ERT
²²⁶ Ra/ ²²² Rn	1.6×10^3 a	DC	α	3.83 d	α	ERT
²²⁵ Ac/ ²¹³ Bi	10.0 d	A, DC	α	45.6 min	β^-, α	ERT

Note: Nuclear decay data from Browne and Firestone [1.21].

^a Abbreviations are as follows: A: accelerator; DC: decay chain; f: fission; R: reactor/neutron capture; R(f): reactor/fission product.

^b Abbreviations are as follows: Ae: atomic electrons; EC: electron capture; IT: isomeric transition; β^+ : if EC < 50%.

^c Abbreviations are as follows: ERT: endoradiotherapy; FPRNA: first pass radionuclide angiography; PET: positron emission tomography; RPC: radiopharmaceutical chemistry; SPECT: single photon emission computerized tomography.

combination of decay modes. Consequently, the applications of generators vary depending on the decay characteristics, including the half-life of the daughter radionuclide.

Generator produced positron emitters. There are several radionuclide generator systems with longer lived parent radionuclides offering neutron deficient daughter radionuclides, which decay via positron emission or electron capture. Some of the daughter radionuclides are short lived, such as ⁸²Rb ($T_{1/2}$: 1.27 min), and others are longer lived, such as ⁴⁴Sc ($T_{1/2}$: 3.93 h) and ⁶⁸Ga ($T_{1/2}$: 1.14 h). Among the radionuclide generator systems with longer lived parents, the ⁶⁸Ge/⁶⁸Ga and ⁸²Sr/⁸²Rb generators are currently the most widely used. Gallium-68 is emerging as a very important radionuclide for the development of PET radiopharmaceuticals.

Generator produced photon emitters. In addition to the ⁹⁹Mo/^{99m}Tc radionuclide generator system, there is continued interest in the availability of radionuclide generator systems for evaluation of pulmonary ventilation and cardiac function. However, ultra-short-lived generator derived radionuclides ($T_{1/2} < 1-2$ min) currently are not widely used for first pass radionuclide angiography (FPRNA) to evaluate ventricular function (wall motion). The commercially available ⁸¹Rb/^{81m}Kr generator is used for pulmonary ventilation studies as well as for evaluation of the right ventricular chamber. This generator system is approved for human use in Europe.

Other generator systems that provide ultra-short-lived daughter radionuclides for FPRNA include the ^{195m}Hg ($T_{1/2}$: 1.73 d)/ ^{195m}Au ($T_{1/2}$: 30.5 s) and ^{191}Os ($T_{1/2}$: 15.4 d)/ ^{191m}Ir ($T_{1/2}$: 4.94 s) generators. More recently, the ^{178}W ($T_{1/2}$: 21.5 d)/ ^{178}Ta ($T_{1/2}$: 9.31 min) generator has been introduced. Long lived parent radionuclide generator systems include the ^{109}Cd ($T_{1/2}$: 1.267 a)/ ^{109m}Ag ($T_{1/2}$: 39.6 s) and ^{113}Sn ($T_{1/2}$: 115.09 d)/ ^{113m}In ($T_{1/2}$: 1.658 h) generators.

Generator produced particle emitters for therapy. Generator derived therapeutic radionuclides have a number of characteristic decay properties and can emit beta particles, Auger electrons, low energy photons and alpha particles. Key examples of therapeutic radionuclide generators obtained from reactor produced parent radionuclides include ^{90}Sr ($T_{1/2}$: 28.6 a)/ ^{90}Y ($T_{1/2}$: 64.1 h) and ^{188}W ($T_{1/2}$: 69 d)/ ^{188}Re ($T_{1/2}$: 16.9 h). Examples of generators that provide alpha emitting daughter radionuclides include the ^{225}Ac ($T_{1/2}$: 10 d)/ ^{213}Bi ($T_{1/2}$: 45.6 min) and ^{224}Ra ($T_{1/2}$: 3.66 d)/ ^{212}Pb ($T_{1/2}$: 10.64 h)/ ^{212}Bi ($T_{1/2}$: 1.01 h) generator systems.

Table 1.2 provides examples of key radionuclide generators that provide daughter radionuclides for diagnostic or therapeutic applications in nuclear medicine.

1.1.4. General considerations for the use of a generator

The activity of the daughter radionuclide obtained per elution cycle (batch) is the main parameter for the application of a generator system. The activity of the daughter radionuclide generated at a given time can be calculated using Eqs (1.1)–(1.7). For practical considerations, generators are eluted at periodic

TABLE 1.2. EXAMPLES OF KEY RADIONUCLIDE GENERATOR SYSTEMS USED FOR NUCLEAR MEDICINE APPLICATIONS

Type of equilibrium	Parent ($T_{1/2}$)	Daughter ($T_{1/2}$)	Main decay mode of daughter	$T_{1/2,1}:T_{1/2,2}$
Secular	^{68}Ge (270 d)	^{68}Ga (68 min)	β^+	5.7×10^2
	^{90}Sr (28.6 a)	^{90}Y (64.1 h)	β^-	3.9×10^2
	^{82}Sr (25.6 d)	^{82}Rb (1.27 min)	β^+	2.9×10^2
	^{81}Rb (4.58 h)	^{81m}Kr (13 s)	γ	1.3×10^2
	^{188}W (69 d)	^{188}Re (16.9 h)	β^-	9.8×10^1
	^{62}Zn (9.26 h)	^{62}Cu (9.74 min)	β^+	5.7×10^1
Transient	^{99}Mo (2.75 d)	^{99m}Tc (6.0 h)	γ	3.0×10^0
	^{166}Dy (3.40 d)	^{166}Ho (1.117 d)	β^-	1.1×10^0

intervals depending on the daughter activity requirements. Many times, the separation of the daughter from the parent may not occur at the time the daughter activity is at its maximum as calculated using Eq. (1.7). When the daughter product is too short lived, much of the activity is not eluted and decays in the generator. When the daughter product is long lived, periodic elution will take place prior to peaking of the daughter activity.

Depending on the chemical design of a radionuclide generator system, elution efficiencies vary and can result in separation of less than 100% of the daughter activity formed. In addition, with an increasing number of separations and storage, the elution efficiency may drop further for chemical, physicochemical or radiolytic reasons.

Radionuclide generators represent a cost effective strategy for obtaining daughter radionuclides, provided the generator is used effectively. Other advantages are the ease with which the daughter product can be separated on demand and the availability of the daughter radionuclide in a high specific activity, no-carrier-added form. The availability of short lived radionuclides from radionuclide generators is particularly important in those areas far from isotope production facilities. A large number of the nuclear medicine studies performed in many parts of the world would not have been possible without the availability of radionuclide generators.

Radionuclide generators intended for applications for clinical use must meet regulatory and quality control requirements. The production of the radionuclide generator parent, its separation from the target material, and the chemical and technical construction of the radionuclide generator are factors that result in a generator which is efficient and easy to operate. Processes for the production of radionuclide generator systems for clinical applications generally should follow good manufacturing practice standards.

1.2. OBJECTIVE

This publication provides the detailed information required for production and chemical processing of a select number of radionuclides that serve as the parent in generator systems used to obtain daughter radionuclides of medical interest. The information contained herein should enable the reader to understand the routes of production, radiochemical processing and quality evaluation of the parent radionuclides. The references included in the individual chapters of this report can serve as background for preparing documentation on the production and/or use of these generator systems.

The production of the selected parent radionuclides involves accelerators or research reactors, with the associated infrastructure requirements, including

chemical processing and waste handling facilities, which in general are only available at large national or regional facilities.

1.3. SCOPE

This publication is limited to four generator systems that have long lived ($T_{1/2} > 25$ d) parent radionuclides and whose use in research and clinical settings is well established. It aims to provide the information required to produce and process the ^{68}Ge , ^{82}Sr , ^{90}Sr and ^{188}W parent radionuclides. The first two of these generator systems provide radionuclides that are useful in PET; the latter two provide radionuclides for therapeutic applications. Germanium-68 and ^{82}Sr are produced using accelerators, ^{188}W is produced by neutron activation in a reactor, and ^{90}Sr is a fission product available from spent fuel.

1.4. STRUCTURE

Following this introductory chapter are four chapters describing the production routes for and process chemistry of the selected parent radionuclides: ^{68}Ge , ^{82}Sr , ^{90}Sr and ^{188}W . Each chapter provides an introduction containing information on the use of the generator system, a section on the physical and chemical characteristics, and a section on production and processing methods, including relevant separation approaches.

REFERENCES TO CHAPTER 1

- [1.1] BRUCER, M., Medical radioisotope cows, *Isot. Radiat. Tech.* **3** (1965) 1.
- [1.2] STANG, L., *Radionuclide Generators: Past, Present and Future*, Rep. BNL 50186, T-541, Brookhaven National Laboratory, New York (1969).
- [1.3] LEBOWITZ, E., RICHARDS, P., Radionuclide generator systems, *Sem. Nucl. Med.* **4** (1974) 257.
- [1.4] LIESER, K.H., Chemische Gesichtspunkte für die Entwicklung von Radionuklidgeneratoren, *Radiochim. Acta* **23** (1976) 57.
- [1.5] YANO, Y., "Radionuclide generators: Current and future applications in nuclear medicine", *Radiopharmaceuticals* (SUBRAMANIAN, G., RHODES, B.A., COOPER, J.F., SOOD, V.J., Eds), Society of Nuclear Medicine, New York (1978) 236–245.
- [1.6] BOYD, R.E., in *Seminar on Radionuclide Generator Technology*, Paper 21, IAEA-Sr. 131, International Atomic Energy Agency, Vienna, 1986.

- [1.7] BOYD, R.E., HETHERINGTON, E.L.R., MOORE, P.W., “Radionuclide Generator Technology — Status and Prospects”, Radiopharmaceuticals and Labelled Compounds (Proc. Int. Conf. Tokyo, 1984), IAEA, Vienna (1985).
- [1.8] MANI, R.S., Reactor production of radionuclides for generators, *Radiochim. Acta* **41** (1987) 103.
- [1.9] LAMBRECHT, R.M., SAJJAD, M., Accelerator-derived radionuclide generators, *Radiochim. Acta* **43** (1988) 171.
- [1.10] RUTH, T.J., PATE, B.D., ROBERTSON, R., PORTER, J.K., Radionuclide production for the biosciences, *Nucl. Med. Biol.* **16** (1989) 323.
- [1.11] KNAPP, F.F., Jr., MIRZADEH, S., The continuing important role of radionuclide generator systems for nuclear medicine, *Eur. J. Nucl. Med.* **21** (1994) 1151.
- [1.12] MIRZADEH, S., KNAPP, F.F., Jr., Biomedical radioisotope generator systems, *J. Radioanal. Nucl. Chem.* **203** (1996) 471.
- [1.13] LAMBRECHT, R.M., TOMIYOSHI, K., SEKINE, T., Radionuclide generators, *Radiochim. Acta* **77** (1997) 103.
- [1.14] RÖSCH, F., KNAPP, F.F., Jr., “Radionuclide generators”, Handbook of Nuclear Chemistry (VÉRTES, A., NAGY, S., KLENCŠÁR, Z., RÖSCH, F., Eds), Vol. 4, Kluwer Academic Publishers, Dordrecht (2004) 81–118.
- [1.15] LAMBRECHT, R.M., Radionuclide generators, *Radiochim. Acta* **34** (1983) 9.
- [1.16] QAIM, S.M., Cyclotron production of generator radionuclides, *Radiochim. Acta* **41** (1987) 111.
- [1.17] GUILLAUME, M., BRIHAYE, C., Generators for short-lived gamma and positron emitting radionuclides: Current status and prospects, *Int. J. Appl. Radiat. Isot.* **13** (1986) 89.
- [1.18] KNAPP, F.F., Jr., BUTLER T.A. (Eds), Radionuclide Generators: New Systems for Nuclear Medicine Applications, ACS Advances in Chemistry Series No. 241, American Chemical Society, Washington, DC (1984).
- [1.19] GUILLAUME, M., BRIHAYE, C., Generators of ultra-short lived radionuclides for routine application, *Radiochim. Acta* **41** (1987) 119.
- [1.20] INTERNATIONAL ATOMIC ENERGY AGENCY, Therapeutic radionuclide generators: $^{90}\text{Sr}/^{90}\text{Y}$ and $^{188}\text{W}/^{188}\text{Re}$ generators, Technical Reports Series No. 470, IAEA, Vienna (2009).
- [1.21] BROWNE, E., FIRESTONE, R.B., in Table of Radioactive Nuclides (SHIRLEY, V.S., Ed.), John Wiley and Sons, New York (1986).

Chapter 2

PRODUCTION, RADIOCHEMICAL PROCESSING AND QUALITY EVALUATION OF ^{68}Ge

F. ROESCH

Institute of Nuclear Chemistry,
University of Mainz,
Mainz, Germany

D.V. FILOSOFOV

Joint Institute for Nuclear Research, LNP,
Dubna, Russian Federation

2.1. INTRODUCTION

The first application of ^{68}Ge was as a long lived positron source for attenuation correction and calibration of PET scanners. However, with the introduction of positron emission tomography/computed tomography (PET/CT), attenuation correction is now done with X rays rather than with a radioactive source. Currently, interest is growing in the use of ^{68}Ge as the parent radionuclide for the preparation of $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generators. In these applications, the relevant radiation source is ^{68}Ga , which provides 89% positron branching accompanied by low photon emission (1077 keV, 3.22%) [2.1–2.4].

Radioactive reference sources are necessary for quality assurance in PET systems for calibration and transmission measurements. Source sets, consisting of line sources and uniformity phantom(s), are available for the different types of scanner. Line sources are used for transmission scans in order to correct the radiation absorbed by the patient's body, and individual detectors are calibrated by uniformity phantoms and a weakly active rod source.

Recently, the use of $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator systems in nuclear medicine has attracted interest because of the significant potential for PET imaging using ^{68}Ga labelled radiopharmaceuticals. The $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator system may contribute to the clinical impact of nuclear medicine diagnoses for PET much as the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator system did for single photon emission computed tomography (SPECT). A review of the status of radionuclide generator systems in the life sciences, including the $^{68}\text{Ge}/^{68}\text{Ga}$ generator, has recently been published [2.5].

An important characteristic of positron emitting ^{68}Ga is its cyclotron independent availability via the $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator system.

Numerous investigations of $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generators have been undertaken over the past fifty years. A review of this and other PET radionuclide generator systems is provided in Ref. [2.1] and in the references therein.

Today, the most common commercially available $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator is based on a TiO_2 solid phase [2.6]. The generators are provided with ^{68}Ge activities of up to 3.7 GBq. The $^{68}\text{Ga}^{3+}$ is eluted in 0.1N HCl solutions. The ^{68}Ga yield is more than 60% in 5 mL of the eluate, and the ^{68}Ge breakthrough usually does not exceed $5 \times 10^{-3}\%$.

Systematic chemical, radiochemical, technological and radio-pharmaceutical efforts are needed to make a reliable, highly efficient and medically approved $^{68}\text{Ge}/^{68}\text{Ga}$ generator system. The production of the radionuclide generator parent, its separation from the target material, and the chemical and technical concept of the separation of the daughter radionuclide are factors that result in efficient and easy application.

The chemical and technical concepts of the separation of the radionuclide generator daughter $^{68}\text{Ga}(\text{III})$ from its parent radionuclide $^{68}\text{Ge}(\text{IV})$ — that is, development of an optimum separation method providing a high yield of the daughter radionuclide in minimal volumes and with the highest radionuclidic purity (i.e. the lowest breakthrough of the parent nuclide), etc. — are not discussed in this chapter. Other issues that are not addressed here include experimental versus routine buildup of the final generator, consideration of the activity scale with regard to radiation stability (radiolysis) and radiation safety of the long shelf life $^{68}\text{Ge}/^{68}\text{Ga}$ generator system, regulatory requirements and commercial logistics, and eventual recovery of the parent radionuclide.

Finally, relevant aspects of efficient and easy handling of the initial $^{68}\text{Ge}/^{68}\text{Ga}$ generator eluates are included in the context of chemical impurities. Depending on the use of ^{68}Ga , the generator system may require sophisticated post-elution processing of the initial ^{68}Ga eluate to achieve the required chemical, radiochemical and radionuclidic purity of ^{68}Ga to allow for efficient synthesis of ^{68}Ga radiopharmaceuticals and to meet the requirements of drug preparations.

2.2. BACKGROUND

2.2.1. Production of ^{68}Ge

The parent radionuclide ^{68}Ge is produced in an accelerator using a variety of potential nuclear reactions. The investigation of precise nuclear data is mandatory for optimum production parameters that provide the corresponding thick target yields and the desired radionuclidic purity. The basics of cyclotron based production of the parent radionuclide are discussed in detail in, for

example, Ref. [2.7]. The discussion here includes some of the chemical and technological features of high flux irradiations with sophisticated target design at adequate irradiation facilities, the costs of target materials, in particular of the enriched target isotopes that are required, and the specific activity of the ^{68}Ge produced.

2.2.2. Selection of a method for separation of parent radionuclide from target material

In this chapter, the optimum chemical forms of the target material for the most relevant ^{68}Ge production routes are discussed. The principal methods for separation of ^{68}Ge (ion exchange, extraction, volatilization, precipitation, etc.) allowing high chemical separation yields of the parent radionuclide are also discussed.

2.2.3. Early developments and applications of the $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator

Early generator systems separated ^{68}Ga as an EDTA complex from ^{68}Ge , absorbed on alumina or zirconium oxides [2.8]. Analogously, ^{68}Ge was retained on antimony oxide Sb_2O_5 , and ^{68}Ga was eluted with oxalate solutions [2.9]. Anion exchange resins using dilute hydrofluoric acid solutions as an eluent allowed high purity separations due to the significant differences in distribution coefficients of the elements [2.10]. The breakthrough of ^{68}Ge was $<10^{-4}$ for up to 600 elutions, and the ^{68}Ga yield was $>90\%$. In all these cases, further application of the generator eluate for ^{68}Ga labelling reactions was not possible or was difficult. Consequently, ‘ionic’ $^{68}\text{Ge}/^{68}\text{Ga}$ generators were developed, providing $^{68}\text{Ga}^{3+}$ eluates. In these cases, ^{68}Ge was absorbed on inorganic matrices such as alumina, $\text{Al}(\text{OH})_3$ and $\text{Fe}(\text{OH})_3$ [2.11, 2.12], SnO_2 , ZrO_2 , TiO_2 [2.13], and CeO_2 [2.14, 2.15]. SnO_2 showed the best parameters in terms of ^{68}Ge breakthrough (10^{-6} – $10^{-5}\%$ per bolus) and a $^{68}\text{Ga}^{3+}$ elution efficiency of 70–80% in 1M hydrochloric acid [2.16].

Alternatively, Ge(IV) is known to form very stable complexes with phenolic groups [2.17], and its adsorption on a 1,2,3-trihydroxybenzene (pyrogallol)-formaldehyde resin was utilized [2.18, 2.19]. Average yields of ^{68}Ga of 75% during a period of 250 d were reported [2.18]. The Ge breakthrough was <0.5 ppm, with no detectable radiolytic by-products for a 370 MBq (10 mCi^1)

¹ $1 \text{ Ci} = 3.7 \times 10^{10} \text{ Bq}$.

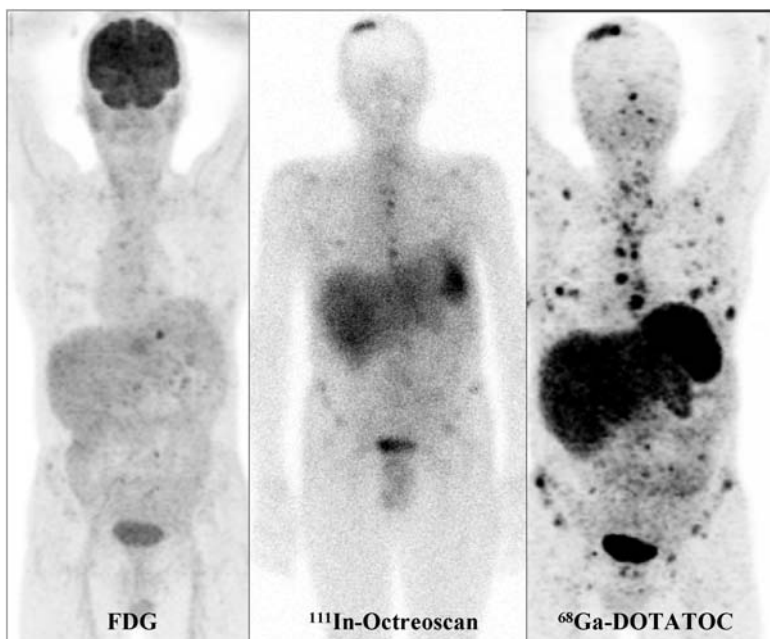


FIG. 2.1. PET/CT molecular imaging of neuroendocrine tumours using ^{68}Ga -DOTATOC (right) compared with ^{111}In -octreoscan SPECT (centre) and ^{18}F -FDG (left) [2.25].

generator. The pyrogallol-formaldehyde resin was found to be resistant to dissociation from radiation [2.19].

The early generator systems, which separated ^{68}Ga as an EDTA complex from ^{68}Ge [2.8], provided neutral $[\text{}^{68}\text{Ga}]\text{EDTA}$ solutions. The $[\text{}^{68}\text{Ga}]\text{EDTA}$ was injected directly, in an attempt to image tumours. The next application of ^{68}Ga was as a $[\text{}^{68}\text{Ga}]\text{BAT-TECH}$ agent for myocardial perfusion [2.20]. Recently, significant potential has been developed for PET imaging of neuroendocrine tumours using $[\text{}^{68}\text{Ga}]\text{DOTA-DPhe}^1\text{-Tyr}^3\text{-octreotide}$ (^{68}Ga -DOTATOC) [2.21]. The octapeptide octreotide derivative showed high affinity to the *ssr2* subtype of somatostatin receptor expressing tumours, and the conjugated macrocyclic bifunctional chelator DOTA binds the trivalent $^{68}\text{Ga}^{3+}$ with high thermodynamic and kinetic stability. Despite the short half-life of ^{68}Ga , the tracer allows excellent visualization of tumours and small metastases. Figure 2.1 shows the images obtained with ^{18}F -FDG, ^{111}In -octreotide and ^{68}Ga -DOTATOC. There is enormous interest in ^{68}Ga -DOTATOC and a similar ^{68}Ga labelled radiopharmaceutical, ^{68}Ga -DOTA-NOC, for PET imaging of neuroendocrine tumours [2.22].

Another interesting and potentially important application of ^{68}Ga derived from $^{68}\text{Ge}/^{68}\text{Ga}$ generators is its use in liquid filled angioplasty balloons to inhibit arterial restenosis following coronary angioplasty [2.22, 2.24].

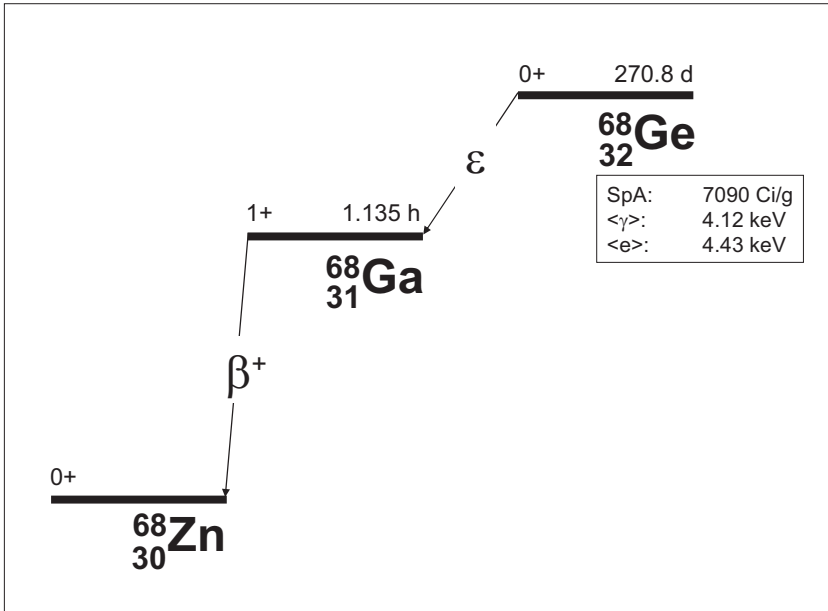


FIG. 2.2. The principal decay scheme of ^{68}Ge [2.1]. Note: $1 \text{ Ci} = 3.7 \times 10^{10} \text{ Bq}$; SpA: theoretical maximum specific activity; $\langle \gamma \rangle$: average electromagnetic radiation energy per disintegration; $\langle e \rangle$: average electron energy per disintegration.

2.3. NUCLEAR DECAY CHARACTERISTICS

The parent radionuclide ^{68}Ge decays via electron capture to ^{68}Ga ($T_{1/2}$: 270.95 d). The ^{68}Ga that is formed subsequently decays ($T_{1/2}$: 67.71 min) to stable ^{68}Zn . Gallium-68 is a positron emitter with 89% positron branching accompanied by low photon emission (1077 keV, 3.22%) [2.1–2.4]. The ^{68}Ge itself does not emit significant photon radiation (Fig. 2.2).

2.4. ^{68}Ge PRODUCTION

2.4.1. Overview

Germanium-68 can be produced via a number of nuclear reaction pathways, all using charged particle induced reactions in particle accelerators. The most relevant processes are listed in Table 2.1, categorized according to the type of particle utilized. The reaction pathways are schematically illustrated in Fig. 2.3 (reactions 1, 2 and 6) and in Fig. 2.4 (reaction 3). Deuterium or ^3He induced

TABLE 2.1. OVERVIEW OF THE MOST RELEVANT NUCLEAR REACTIONS YIELDING ^{68}Ge

Particle	Nuclear reaction	Target nucleus	Reaction No.
Proton	(p,2n)	^{69}Ga	1
Proton	(p,xn), $x = 2, 4$	$^{\text{nat}}\text{Ga}$ ($^{69,71}\text{Ga}$)	2
Proton	(p,pxn)	$^{\text{nat}}\text{Ge}$	3
Proton	(p,xnyp), $y = 2, 4, 6, \dots$	^{75}As , $^{79,81}\text{Br}$, $^{85,87}\text{Rb}$	4
Deuteron	(d,3n)	^{69}Ga	5
Helium-4	(α ,2n)	^{66}Zn	6
Helium-3	(^3He ,xn), $x = 1, 2, 3$	$^{66,67,68}\text{Zn}$	7

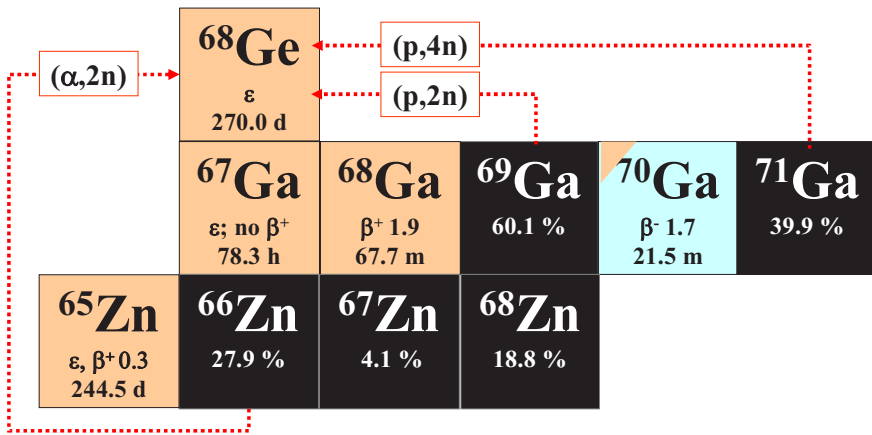


FIG. 2.3. Excerpt of the Karlsruhe nuclide chart and indication of the processes $^{69}\text{Ga}(p,2n)$ and $^{\text{nat}}\text{Ga}(p,xn)$ (represented by $^{69}\text{Ga}(p,2n) + ^{71}\text{Ga}(p,4n)$ reactions) and $^{66}\text{Zn}(\alpha,2n)$.

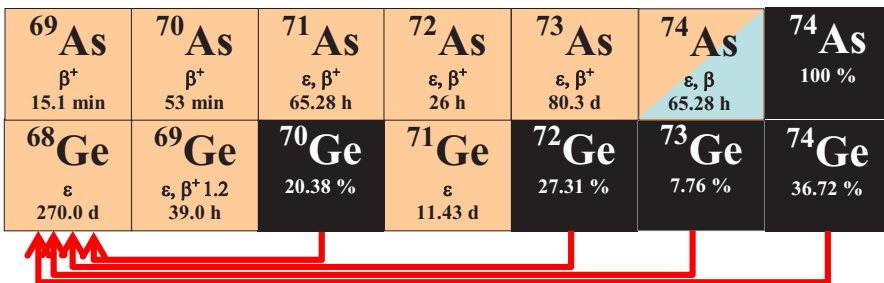


FIG. 2.4. Excerpt of the Karlsruhe nuclide chart and indication of the proton induced processes of (p,pxn) reactions on Ge targets.

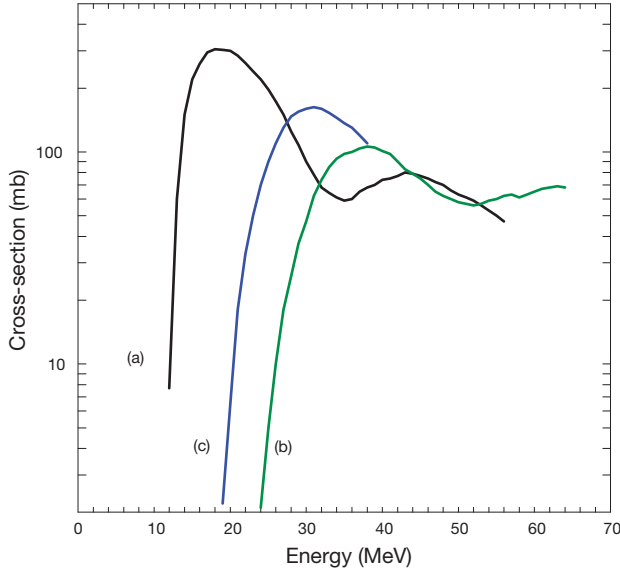


FIG. 2.5. Comparison of various excitation functions for the (a) $Ga(p,xn)^{68}Ge$, (b) $Ge(p,pxn)^{68}Ge$ and (c) $Zn(\alpha,xn)^{68}Ge$ reactions [2.37].

processes on Ga (reaction 5) and Zn (reaction 7) targets are not shown, as they represent analogues to the proton (reaction 1) and 4He (reaction 6) induced processes.

2.4.2. Nuclear reactions

A variety of nuclear reaction pathways are possible for production of ^{68}Ge . To estimate which are the most useful, detailed measurement of individual excitation functions is mandatory. In fact, a number of literature data are available on individual nuclear reactions and/or on systematic comparisons in terms of both experiments and theory [2.25–2.36]. Horiguchi et al. [2.37] provide excitation functions and thick target yields for the $Ge(p,pxn)^{68}Ge$ reactions and compare them with those of the $Ga(p,xn)^{68}Ge$ and $Zn(\alpha,xn)^{68}Ge$ reactions. Figures 2.5 and 2.6 show the corresponding excitation functions; Figs 2.7 and 2.8 give thick target yields. In Figs 2.5 and 2.7, curve (a) is the excitation function for the Ga target converted from cross-sections for the $^{69,71}Ga(p,xn)^{68}Ge$ reactions given in Ref. [2.28]; curve (b) is the excitation function for the $Ge(p,pxn)^{68}Ge$ reactions [2.37]; and curve (c) is the excitation function for the $Zn(\alpha,xn)^{68}Ge$ reactions given in Ref. [2.29].

As the proton energy increases, the cross-sections decrease rapidly. More recently, the IAEA has tried to define ‘recommended’ cross-section data for the

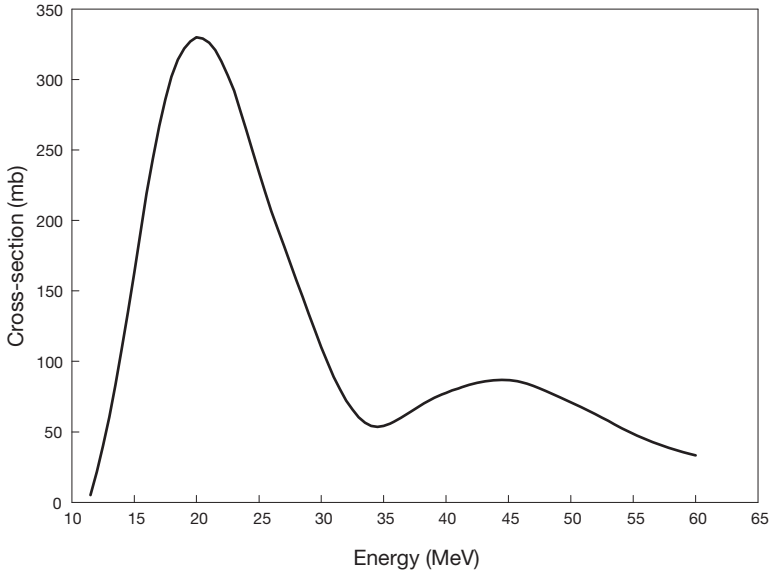


FIG. 2.6. IAEA recommended excitation function for the $^{nat}\text{Ga}(p,xn)^{68}\text{Ge}$ reactions [2.35].

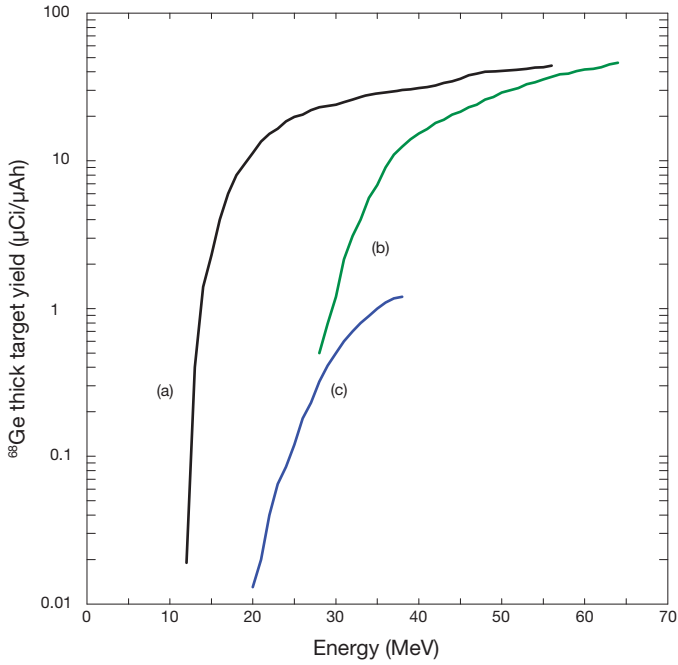


FIG. 2.7. Comparison of thick target yields for the (a) $\text{Ga}(p,xn)^{68}\text{Ge}$, (b) $\text{Ge}(p,pxn)^{68}\text{Ge}$ and (c) $\text{Zn}(\alpha,xn)^{68}\text{Ge}$ reactions [2.37].

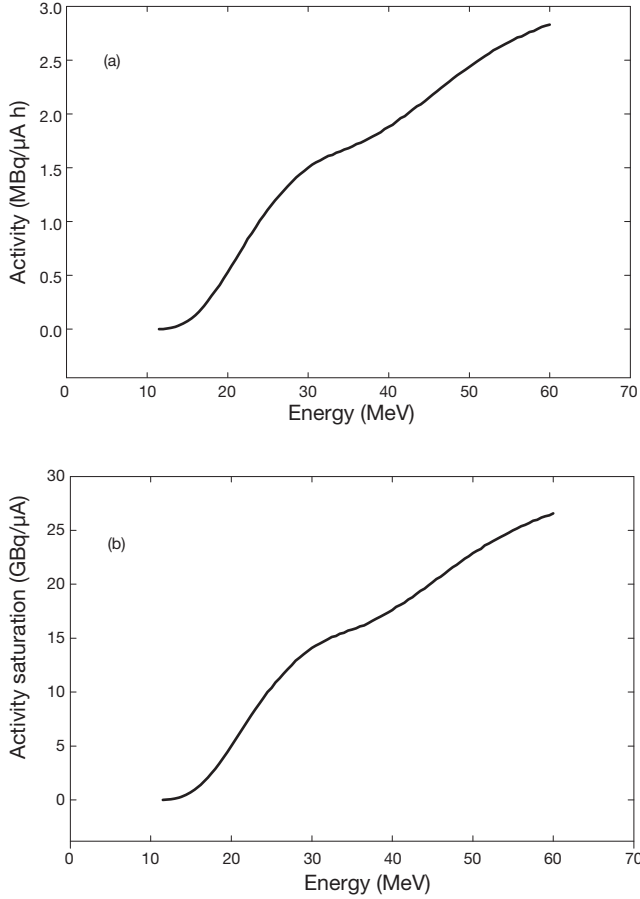


FIG. 2.8. Thick target yields for the $^{nat}\text{Ga}(p,2n)$ reactions [2.35], calculated for (a) a 1 h irradiation as well as for (b) saturation.

$\text{Ga}(p,2n)$ process [2.34]. Utilizing available data in the computerized database EXFOR, cross-sections for the $^{69}\text{Ga}(p,2n)$ process were calculated [2.26, 2.28] by the nuclear reaction model code ALICE IPPE and by two fitting procedures, Padé and Spline. The ALICE model calculation gave cross-sections that were too high. The best approximation was judged to be the Padé fit. Table 2.2 lists the cross-sections for the $^{69}\text{Ga}(p,2n)$ process, based on 100% isotopic purity of ^{69}Ga . Analogous results for the $^{nat}\text{Ga}(p,xn)$ processes on a natural Ga target were calculated by the nuclear reaction model code SPEC and by the fitting procedure Spline. The recommended cross-section curve is illustrated in Fig. 2.6; the corresponding yields are shown in Fig. 2.8.

TABLE 2.2. IAEA RECOMMENDED CROSS-SECTION VALUES FOR THE $^{69}\text{Ga}(p,2n)^{68}\text{Ge}$ REACTION [2.35]

Energy (MeV)	Cross-section (mb)	Energy (MeV)	Cross-section (mb)	Energy (MeV)	Cross-section (mb)	Energy (MeV)	Cross-section (mb)
13.0	97.7	20.0	600	27.0	339	34.0	86.6
13.5	114	20.5	596	27.5	309	34.5	80.8
14.0	149	21.0	590	28.0	280	35.0	75.7
14.5	207	21.5	582	28.5	253	35.5	71.1
15.0	279	22.0	571	29.0	228	36.0	67.3
15.5	356	22.5	559	29.5	205	36.5	64.1
16.0	427	23.0	544	30.0	184	37.0	61.4
16.5	486	23.5	526	30.5	165	37.5	59.0
17.0	531	24.0	505	31.0	149	38.0	57.0
17.5	563	24.5	482	31.5	135	38.5	55.3
18.0	584	25.0	456	32.0	122	39.0	53.8
18.5	595	25.5	428	32.5	111	39.5	52.5
19.0	601	26.0	399	33.0	102	40.0	51.4
19.5	602	26.5	369	33.5	93.6		

In contrast, the $\text{Ge}(p,pxn)$ reaction cross-sections decrease less and remain almost constant at higher proton energies. This is particularly relevant since natural Ge contains many stable isotopes, from ^{70}Ge to ^{76}Ge (Fig. 2.4). In particular, the excitation function for the $\text{Ge}(p,pxn)^{68}\text{Ge}$ reactions tends to increase even above the 64 MeV proton energy. The reason is that the $^{74}\text{Ge}(p,p6n)^{68}\text{Ge}$ reaction takes place in this energy region, and in higher energy regions the $^{76}\text{Ge}(p,p8n)^{68}\text{Ge}$ reaction is still possible. Consequently, a large yield of ^{68}Ge is expected for the $\text{Ge}(p,pxn)$ reactions. The specific activity of ^{68}Ge produced in these processes, however, is significantly lower than that for the proton induced reactions on Ga targets. In parallel, radioarsenic isotopes are also formed according to $\text{Ge}(p, xn)$ processes.

2.4.3. Thick target yields

From the excitation functions shown in Fig. 2.7, integral ^{68}Ge thick target yields have been calculated [2.37] for natural metallic Ge and Zn as well as Ga_2O_3 targets. The yields are larger for proton induced reactions on Ga than on

Ge targets in the region below 60 MeV, although the latter become larger above 60 MeV. The thick target yields for the Ga(p,2n) reactions have recently been validated [2.35]. Following the excitation function shown in Fig. 2.6, thick target yields per microampere were calculated for a 1 h irradiation as well as for saturation; these yields are shown in Fig. 2.8. The (p,2n) reaction on Ga targets provides significant cross-sections. Experimental thick target yields amount to 0.96/0.53 MBq· $\mu\text{A}^{-1}\cdot\text{h}^{-1}$ at this energy, but reach values of >2 and >1 MBq· $\mu\text{A}^{-1}\cdot\text{h}^{-1}$ at 25 MeV, respectively.

The yield for the Zn(α ,2n) reaction is more than one order of magnitude smaller than the yields for the other reactions, mainly due to the lower cross-section values and the shorter range of alpha particles, which is about one tenth of the proton range. Proton induced spallation reactions on Rb, Br or As target materials again give about one tenth of that yield.

2.4.4. Comparison of production methods described in the literature

Nuclear reactions on Ga targets are the best choice of particle induced nuclear processes for producing no-carrier-added ^{68}Ge . Thus ^{68}Ge production today uses protons. Due to the long half-life of ^{68}Ge , high current accelerators with on-target beam intensities from 40 to more than 100 μA are required for sufficient batch yields (about 37 GBq). In addition, long term irradiation periods of several days are mandatory. Consequently, only a limited number of adequate accelerators are available. The parameters known from the literature for various accelerator sites are summarized in Table 2.3. Routine production is mainly known for Brookhaven National Laboratory (BNL) and Los Alamos National Laboratory (LANL), United States of America (USA); iThemba Laboratories/NAC, Faure, South Africa; and Cyclotron Co., Ltd, Obninsk, Russian Federation. Those production centres report production capacities of about 18.5–74 GBq (0.5–2 Ci) of ^{68}Ge per batch.

At BNL, ^{nat}Ga targets are irradiated with 30 ± 2 MeV at the Brookhaven Linac Isotope Producer (BLIP); 81 g of ^{nat}Ga metal is encapsulated in a Nb container (6.98 cm in diameter, 5.08 mm thick). The target itself acts as a beam stopper at BLIP. For a one month irradiation, overall batch yields are 33.3–51.8 GBq (900–1400 mCi) [2.38]. Chemical processing starts after about a two week period to allow for decay of co-produced short lived radionuclides such as ^{69}Ge and ^{67}Ga . The specific activity of ^{68}Ge is 58 GBq (1.57 ± 0.1 Ci) per milligram of stable Ge. High volume concentrations of >3 GBq per millilitre were achieved by preparing and concentrating ^{68}Ge in the form of its non-volatile DTPA complex. However, this chemical speciation would not be of direct use for the preparation of $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generators for medical application. Germanium-68 is also supplied in chloride form with a radioactivity concentration of >2 GBq per

TABLE 2.3. ^{68}Ge PRODUCTION PARAMETERS FOR VARIOUS ACCELERATOR SITES

Accelerator site	Target	Irradiation parameters				Product activity	
		E_p (MeV)	T (h)	I (μA)	Power (mAh)	A (GBq)	Yield (Ci/Ah)
Cyclotron Co., Ltd, Obninsk [2.6]	Ga_4Ni on Cu backing	23	120–240				
iThemba Laboratories/NAC [2.41, 2.42]	4.0 g Ga in 5.2 g Nb	36			37	16.6	
	4.5 g Ga_2O in Al	2–34		65			15.1
Brookhaven National Laboratory [2.38]	81 g Ga in Nb	30	640	85	45–55	33–51	
Los Alamos National Laboratory [2.39, 2.40]	4 g Ga in 5 g Nb (part of stack)	~60	492	125		70	32
Institute of Nuclear Physics, Kazakhstan [2.43, 2.44]	5 g Ga in Nb	30		40	14	12.4	
Institute for Nuclear Research, Moscow [2.45]	Ga	50–15	250			18.5	
Orsay [2.46]	3 mm Ga_4Ni in Ti (24 μm)	20(19.5)	60	45			9.2

millilitre. The overall Ga separation factor is 1.1×10^6 , which is about 80 μg of Ga remaining, corresponding to 0.085 μg of Ga per millicurie of ^{68}Ge produced. The radionuclidic purity is >99.9%. Metallic impurities are Zn (2 ppm), Nb (<7 ppm) and Cu, Pb, Co, Cr, Cd, Ni, Fe, Mn and Al (all <1 ppm).

At LANL, a new Isotope Production Facility (IPF) became operational in 2005. At the IPF, 100 MeV protons are delivered into a stack system of various targets, which are irradiated with individual optimum proton energies of approximately 90, 65 or 40 MeV [2.39]. About 4 g of ^{nat}Ga metal inside a ~5 g Nb encapsulation is irradiated for 20.2 or 16.5 d with a 125 μA proton beam intensity. The production rate is 1.18 MBq (0.032 mCi)/ μAh ; the batch yield at end of bombardment (EOB) is about 70 or 55 GBq. Chemical processing starts two weeks later. Germanium-68 is extracted into CCl_4 and re-extracted into water. Long lived radionuclidic impurities such as ^{88}Zr and ^{88}Y are removed using alumina column chromatography [2.40].

At the iThemba Laboratories/NAC, Ga/Ga₂O₃ targets are initially irradiated with 66 MeV protons, the on Ga target energy being 34 → 0 or 34 → 2.4 MeV. The Ga mass is about 5 g with a thickness of 4 mm. The radionuclidic purity of the processed ⁶⁸Ge is >99.9%. The final product contains <1 µg of Ga per 37 MBq (1 mCi) of ⁶⁸Ge [2.41]. At Cyclotron Co., Ltd., Obninsk, Russian Federation, Ga-Ni alloys are used as the target material, prepared on Cu backings. Irradiations are performed at a rather high proton beam intensity of several hundred microamperes at 23 MeV proton energy. Germanium-68 of a high specific activity (>74 GBq (>2 Ci)/mg) and 99.8% radionuclidic purity is obtained [2.6].

2.4.5. Targetry

The chemical and mechanical design of the target are crucial issues, mainly owing to the thermal aspects of high current irradiations, as the power dissipated in the targets reaches values of about 300–1000 W or more. It is mandatory to provide sufficient cooling for thermal stability of a given target. Thus the main criteria are adequate thermal properties such as the melting points, boiling points and heat transfer coefficients of the target materials and their cooling systems. Other criteria are corrosion and radiation resistance. For Ga(p,xn) production routes, potentially useful target compounds include Ga₂O₃ (melting point: 1900°C) and Ga₄Ni alloy (melting point: 900°C) [2.6]. Mixtures of Ga metal and Ga₂O₃ have been used, as has Ga₂O [2.42]. However, Ga metal (melting point: 39°C) itself is used as a target. In this case, appropriate containments are required. Usually, Ga encapsulated in Nb containers is used [2.38–2.41, 2.43–2.45]. Corrosion resistant Nb allows effective water cooling of the target. Ga₄Ni is used in cases with proton energy of about 20 MeV [2.6, 2.46]. Loc'h et al. [2.46] provide a detailed description of the preparation and processing of this target. They prepared 15 g of Ga₄Ni with a thickness of 3 mm between a Cu backing and a Ti foil placed in the direction of the proton beam. During irradiation, the target was cooled at the back side of the Cu body by water and at the Ti foil front by He gas flow.

Ga₂O₃ was used as thin samples between Ni and Al foils as a target in those cases where only a low proton beam current was needed for cross-section determinations rather than higher beam intensities for production processes [2.27, 2.28]. Irradiation of Ga as oxide (Ga₂O₃) prohibits the use of high particle currents, since absorbed energy dissipation is inadequate and such targets deteriorate quickly. Naidoo et al. [2.47] developed Ga₂O targets as discs 20 mm in diameter and 1 mm thick. These discs are encapsulated in an Al canister, which is sealed by cold welding.

2.5. CHEMICAL ASPECTS

In this section, chemical aspects of producing ^{68}Ge related to the Ga(p,xn) type proton induced nuclear processes are discussed, as these are the most relevant production routes.

2.5.1. Chemical separations

Several scientific papers describe in detail a variety of chemical procedures. Principal techniques include distillation of ^{68}Ge as tetrachloride (e.g. Refs [2.30, 2.48]), ion exchange chromatography (e.g. Refs [2.47, 2.49]) and liquid–liquid extraction (e.g. Refs [2.12, 2.13, 2.42, 2.46, 2.50]). The separation technique most often applied today is liquid–liquid extraction using CCl_4 [2.6, 2.38, 2.40]. For Ga/Nb systems, ^{68}Ge is extracted into CCl_4 after dissolution of the target in 12M H_2SO_4 (with the aid of HCl and H_2O_2). Germanium-68 is back-extracted into 0.05N HCl and evaporated to the appropriate volume [2.41]. For Ga_4Ni targets, semi-automated processing consisting of electrochemical target dissolution is used. Following extraction of ^{68}Ge from 9.0–9.5M HCl into CCl_4 , the ^{68}Ge is back-extracted into water [2.6].

2.5.2. Purity of ^{68}Ge as produced in Ga(p,xn) reactions

Quality control of ^{68}Ge batches considers both chemical and radionuclidic purity aspects, as well as estimation of specific activity. A central issue is the specific activity of ^{68}Ge . Two facilities provide the corresponding parameters, namely, 58 GBq/mg [2.38] and >74 GBq/mg [2.6]. Alpha induced processes on Zn targets should provide specific activities significantly less than 1 Ci per milligram, while specific activities obtained for proton induced productions on Ge targets are orders of magnitude less.

Radionuclidic impurities may be divided into short lived and long lived radionuclides, co-produced mainly within the materials of the encapsulated target (in the case of Nb containments) or backing (i.e. Ni or Cu in the case of Ga_4Ni alloys with Cu backings) used as target materials. Typical examples of long lived contaminations are ^{88}Y ($T_{1/2}$: 106.6 d) and ^{88}Zr ($T_{1/2}$: 83.4 d). When irradiations are performed at proton energies above 40 MeV, ^{65}Zn ($T_{1/2}$: 244.3 d), ^{57}Co ($T_{1/2}$: 271.8 d) and ^{58}Co ($T_{1/2}$: 170.9 d) are formed, in addition to short lived radionuclides such as ^{69}Ge ($T_{1/2}$: 39 h) and ^{67}Ga ($T_{1/2}$: 78.3 h). Most of the short lived radionuclides decay to insignificant percentages within the cooling periods (of up to two weeks) after EOB. Long lived radionuclides and the remaining short lived radionuclides are chemically separated in the processes to isolate ^{68}Ge from the target materials. The final radionuclidic contaminations are analysed by means of quantitative

radioactive assays; that is, gamma ray spectroscopy on semi-conductor detectors. For most of the Ga(p,xn) processes described, an overall radionuclidic purity of ^{68}Ge of >99.9% [2.39, 2.41] or 99.8% [2.6] is obtained.

However, the values given above do not take into account the presence of ^{71}Ge ($T_{1/2}$: 11.43 d) as a co-product of ^{68}Ge in (p,xn) reactions on Ga targets of natural isotopic composition ^{69}Ga : 60.108% and ^{71}Ga : 39.892%. Thus, at EOB ^{71}Ge activities may be higher than those of ^{68}Ge by a factor of 10–20. In comparison, proton induced reactions on Ge targets result in thick target yields for ^{72}As , ^{69}Ge , ^{66}Ga , ^{71}As , ^{67}Ga , ^{74}As and ^{73}As that are up to three orders of magnitude higher than those for ^{68}Ge . Specific efforts would be needed during radiochemical processing to provide ^{68}Ge fractions of high radionuclidic, radiochemical and chemical purity [2.37].

Chemical considerations are related to the radiochemical separation strategy applied to isolate ^{68}Ge from the target materials as well as from capsules, foils or backings used in the target during irradiation. No-carrier-added ^{68}Ge needs to be separated from macroscopic quantities (several grams) of $^{\text{nat}}\text{Ga}$. However, the Ga remaining in the final ^{68}Ge fraction should not exceed microgram amounts. The traces of Ga remaining will be separated during the $^{68}\text{Ge}/^{68}\text{Ga}$ generator production, as sophisticated radiochemical separation strategies are employed to absorb ^{68}Ge effectively and to elute ^{68}Ga selectively from the generator. First runs of these generators thus will have traces of $^{\text{nat}}\text{Ga}$ together with ^{68}Ga generated from ^{68}Ge . Other chemical non-radioactive impurities arise from the remaining traces of non-Ga target components (i.e. Nb, Ni or Cu). The chemical separation employed reduces the amounts of these impurities to parts per million levels. Further metallic impurities are mainly due to traces of Fe. Quantification of the amounts of metallic impurities is done by inductively coupled plasma mass spectrometry (ICP-MS) or inductively coupled plasma optical emission spectrometry (ICP-OES).

2.5.3. Impact of impurities on the handling of ^{68}Ga eluates

The presence of metallic impurities in the ^{68}Ga eluate is highly relevant and can affect the utility of the product. The $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator systems available today are not necessarily optimally designed for direct application in making diagnostic products for human use. The eluate from the commercial generator still contains measurable levels of long lived ^{68}Ge . In addition, the rather large volume and the relatively high concentration of hydrochloric acid in many cases prevent direct use for labelling reactions. Furthermore, labelling yields and specific activities might not reach maximum values owing to the presence of metallic impurities. For example, significant amounts of Zn(II) are generated from the decay of ^{68}Ga . For a ‘fresh’ 1110 MBq (^{68}Ge) generator, the

number of stable ^{68}Zn atoms generated within one day of an elution is 8.93×10^{13} (i.e. 10 ng of Zn(II)), compared with 4.69×10^{12} atoms of ^{68}Ga in 800 MBq of the ^{68}Ga eluted. In the case of 'fresh' generators, the amount of stable ^{71}Ga generated from the ^{71}Ge decay may be up to one order of magnitude higher than the amount of stable ^{68}Zn generated.

In addition, Ti(IV) or other residuals from the generator column material and Fe(III) are present in the eluate. All these metallic impurities will adversely affect the ^{68}Ga labelling yields as well as the specific activity of the labelled product. Thus, dedicated procedures for processing the eluate from the radionuclide generator, including labelling and purification of ^{68}Ga radiopharmaceuticals, need to be developed. Several approaches to processing generator derived $^{68}\text{Ga(III)}$ are described in Refs [2.21, 2.51–2.54]. Some of these approaches are discussed in the following.

Anion exchange chromatography. Processing of ^{68}Ga eluate from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator is described by Meyer et al. [2.55]. The initial volume of 10 mL of the 0.1N HCl eluate is transferred to a vial containing 15 mL of 9.5N HCl to obtain a final hydrochloric acid concentration of 5.5M. Under these conditions, ^{68}Ga can be adsorbed on a strong anion exchanger as anionic chloro complexes of $^{68}\text{Ga(III)}$. Following a washing step with 1 mL of 5.5N HCl, the resin is flushed with a stream of N and then eluted with H_2O in small volumes [2.51]. This strategy separates ^{68}Ge , but it does not allow *direct* loading of $^{68}\text{Ga(III)}$ on the anion exchange resin from 0.1N HCl, nor does it provide purification of Ga(III) from, for example, Zn(II) and Fe(III). The time needed to process the generator eluate, and to synthesize and purify the labelled product (e.g. ^{68}Ga -DOTA conjugated peptides), reduces the overall yields of the product. A final yield of $46 \pm 5\%$ for the ^{68}Ga labelled DOTA conjugated octreotide has been reported [2.52, 2.55, 2.56].

Fractionation. Another approach to overcoming problems like eluate volume, acidic pH and content of ^{68}Ge and chemical impurities is to fractionate the initial generator eluate [2.53]. This concept utilizes the fact that the eluted ^{68}Ga activity peaks within about 1–2 mL, representing about two thirds of the total activity. In the context of synthesizing ^{68}Ga labelled compounds, decay corrected yields of ^{68}Ga radiopharmaceuticals thus cannot exceed 60–70%. Owing to processing times and labelling efficacies, in practice the effective yields of labelled DOTA conjugated peptides such as ^{68}Ga -DOTATOC amount to about 50% [2.56]. The contents of ^{68}Ge and metallic impurities are lower because of the lower eluate volume used, but principally are not chemically removed prior to the ^{68}Ga labelling steps.

Cation exchange chromatography. The key step in this procedure consists of the direct transfer of the initial 0.1N HCl ^{68}Ga eluate to a cation exchanger. Owing to the high distribution coefficients, ^{68}Ga is quantitatively adsorbed on

only about 50 mg of the resin directly from the generator eluate. Low volumes of 0.4–1.0 mL of hydrochloric acid/acetone mixtures are applied to purify ^{68}Ga from Ge(IV), Ti(IV), Zn(II) and Fe(III). The post-processing takes 4 min, with overall ^{68}Ga recovery yields of $97 \pm 2\%$. This efficient and simplified system for processing ^{68}Ga eluates results in volume reduction along with chemical and radiochemical purification. The procedure leads to almost complete removal of metallic impurities including ^{68}Ge breakthrough, thus providing the purified ^{68}Ga in a form useful for direct labelling, with acceptable pH, volume and purity. The method is adapted for the preparation of a chemistry module that can be used for the preparation of injectable ^{68}Ga labelled radiopharmaceuticals. The steps in the module include processing of the eluate, radiolabelling and purification of the final product in an aseptic condition. The module can be used in a clinical environment for the preparation of ^{68}Ga labelled radiopharmaceuticals. [2.54].

2.6. CONCLUSION

Germanium-68 can be produced via a variety of nuclear reaction pathways. The most effective route appears to be proton irradiation of Ga targets. The high cross-section values of the (p,2n) reaction allow irradiation of natural Ga without isotopic enrichment in ^{69}Ga at medium proton energies of between 20 and 30 MeV. In addition, if protons of higher energies are available, the (p,4n) process on ^{71}Ga contributes to production yields.

High beam intensities in the range of 100 μA or more are required to produce batch activities of >37 GBq of ^{68}Ge . As the number of accelerators with the above features is limited worldwide, the number of ^{68}Ge production sites is also limited. The nuclear centres at LANL, BNL, Obninsk and Faure report successful production. Attempts to establish ^{68}Ge production have recently been reported by a few other centres.

Chemical aspects of production relate to target preparation and radiochemical separation of ^{68}Ge . Metallic Ga encapsulated in Nb containments and Ga_4Ni alloys are the best choices for target materials. Chemical separation is achieved even for the separation of ^{68}Ge from up to 100 g of Ga target materials. The radiochemical technique that is currently preferred consists of liquid–liquid extraction of ^{68}Ge from the dissolved target using CCl_4 . Following back-extraction into water, high separation factors of about 10^6 are achieved. Specific activities obtained reach values of >74 GBq (>2 Ci) of $^{68}\text{Ge}/\text{mg}$. Radionuclidic purity is high owing to the physical decay of the co-produced short lived radionuclides (such as ^{67}Ga and ^{69}Ge) and radiochemical separation of the long lived radionuclides, mainly co-produced within the non-Ga target or target backing materials. Radionuclidic purity of $>99.9\%$ is achieved.

REFERENCES TO CHAPTER 2

- [2.1] BROWNE, E., FIRESTONE, R.B., in Table of Radioactive Nuclides (SHIRLEY, V.S., Ed.), John Wiley and Sons, New York (1986).
- [2.2] BÉ, M.M., et al., Table of Radionuclides: Comments on Evaluations, CEA/DIMIRI/LNHB, Paris (1999).
- [2.3] SCHÖNFELD, E., SCHÖTZIG, U., GÜNTHER, E., SCHRADER, H., Standardisation and decay data of $^{68}\text{Ge}/^{68}\text{Ga}$, Appl. Radiat. Isot. **45** (1994) 955–961.
- [2.4] BURROWS, T.W., Nuclear data sheets for $A = 68$, Nuclear Data Sheets **97** (2002).
- [2.5] RÖSCH, F., KNAPP, F.F., Jr., “Radionuclide generators”, Handbook of Nuclear Chemistry (VÉRTES, A., NAGY, S., KLENCŠÁR, Z., RÖSCH, F., Eds), Vol. 4, Kluwer Academic Publishers, Dordrecht (2003) 81–118.
- [2.6] RAZBASH, A.A., SEVASTIANOV, Y.G., KRASNOV, N.N., LEONOV, A.I., PAVLIKHIN, V.E., “Germanium-68 row of products”, in Proc. 5th Int. Conf. on Isotopes (SICI), Brussels, 2005, Medimond, Bologna (2005) 147–151.
- [2.7] QAIM, S.M., “Cyclotron production of medical radionuclides”, Handbook of Nuclear Chemistry (VÉRTES, A., NAGY, S., KLENCŠÁR, Z., RÖSCH, F. Eds), Vol. 4, Kluwer Academic Publishers, Dordrecht (2003) 47–80.
- [2.8] GREENE, M.W., TUCKER, W.D., An improved gallium-68 cow, Int. J. Appl. Radiat. Isot. **12** (1961) 62–63.
- [2.9] ARINO, H., SKRABA, W.J., KRAMER, H.H., A new $^{68}\text{Ge}/^{68}\text{Ga}$ radioisotope generator system, Int. J. Appl. Radiat. Nuclides **29** (1978) 117–120.
- [2.10] NEIRINCKX, R.D., DAVIS, M.A., Potential column chromatography for ionic Ga-68 II: Organic ion exchangers as chromatographic supports, J. Nucl. Med. **21** (1980) 81.
- [2.11] KOPECKY, P., MUDROVÁ, B., SVOBODA, K., The study of conditions for the preparation and utilization of $^{68}\text{Ge}-^{68}\text{Ga}$ generator, Int. J. Appl. Radiat. Isot. **24** (1973) 73–80.
- [2.12] KOPECKY, P., MUDROVÁ, B., $^{68}\text{Ge}-^{68}\text{Ga}$ generator for the production of ^{68}Ga in an ionic form, Int. J. Appl. Radiat. Isot. **25** (1974) 263–268.
- [2.13] MALYSHEV, K.V., SMIRNOV, V.V., Gallium-68 yield from hydrated zirconium oxide-based generators, Sov. Radiochim. **17** (1975) 137–140.
- [2.14] AMBE, S., Germanium-68-gallium-68 generator with alpha-ferric oxide support, Appl. Radiat. Isot. **39** (1988) 49–51.
- [2.15] BAO, B., SONG, M., A new $^{68}\text{Ge}/^{68}\text{Ga}$ generator based on CeO_2 , J. Radioanal. Nucl. Chem. **213** (1996) 233–238.
- [2.16] LOC’H, C., MAZIÈRE, B., COMAR, D., A new generator for ionic gallium-68, J. Nucl. Med. **21** (1980) 171–173.
- [2.17] KURNEVICH, G.I., VISHNEVSKII, V.B., LOIKO, E.M., Coordination compounds of germanium(IV) with polyhydric phenols and dimethyl sulfoxide, Russ. J. Inorg. Chem. **19** (1974) 693–696.
- [2.18] SCHUMACHER, J., MAIER-BORST, W., A new $^{68}\text{Ge}/^{68}\text{Ga}$ radioisotope generator system for production of ^{68}Ga in dilute HCl, Int. J. Appl. Radiat. Isot. **32** (1981) 31–36.
- [2.19] NEIRINCKX, R.D., KRONAUGE, J.F., GENNARO, G.P., LOBERG, M.D., J. Nucl. Med. **23** (1982) 245.
- [2.20] MATHIAS, C.A., et al., J. Nucl. Med. **32** (1991) 974 (abstract).

- [2.21] HOFFMAN, M., et al., Biokinetics and imaging with the somatostatin receptor PET radioligand ^{68}Ga -DOTATOC: Preliminary data, *Eur. J. Nucl. Med.* **28** (2001) 1751–1757.
- [2.22] WAGNER, H.N., Advancing a molecular theory of disease, *J. Nucl. Med.* **49** (2008) 15N–34N.
- [2.23] STOLL, H.-P., et al., Liquid-filled balloon brachytherapy using ^{68}Ga is effective and safe because of the short 68-minute half-life, *Circulation* **103** (2001) 1793–1798.
- [2.24] STOLL, H.-P., et al., Advantages of short lived positron-emitting radioisotopes for intracoronary radiation therapy with liquid-filled balloons to prevent restenosis, *J. Nucl. Med.* **42** (2001) 1375–1383.
- [2.25] BIHL, H., Katharinenhospital, Stuttgart, Germany, personal communication (2006).
- [2.26] COHEN, B.L., NEWMAN, E., (p, pn) and (p, 2n) cross sections in medium weight elements, *Phys. Rev.* **99** (1955) 718–723.
- [2.27] PORILE, N.T., Simple nuclear reactions of Ga^{69} and Ga^{71} with high-energy protons, *Phys. Rev.* **125** (1962) 1379–1385.
- [2.28] PORILE, N.T., et al., Nuclear reactions of Ga^{69} and Ga^{71} with 13–56 MeV protons, *Nucl. Phys.* **43** (1963) 500–522.
- [2.29] NAGAME, Y., UNNO, M., NAKAHARA, H., MURAKAMI, Y., Production of ^{67}Ga by alpha bombardment of natural zinc, *Int. J. Appl. Radiat. Isot.* **29** (1978) 615–619.
- [2.30] GRANT, P.M., MILLER, D.A., GILMORE, J.S., O'BRIEN, H.A., Medium-energy spallation cross sections, 1. RbBr irradiation with 800 MeV protons, *Int. J. Appl. Radiat. Isot.* **33** (1982) 415–417.
- [2.31] GRÜTTER, A., Cross sections for reactions with 593 and 540 MeV protons in aluminium, arsenic, bromine, rubidium and yttrium, *Int. J. Appl. Radiat. Isot.* **33** (1982) 725–732.
- [2.32] NAGAME, Y., NAKAHARA, H., FURUKAWA, M., Excitation functions for alpha and ^3He particles induced reactions on zinc, *Radiochim. Acta* **29** (1989) 5–12.
- [2.33] MICHEL, R., et al., Cross sections for the production of residual nuclides by low- and medium-energy protons from the target elements C, N, O, Mg, Al, Si, Ca, Ti, V, Mn, Fe, Co, Ni, Cu, Sr, Y, Zr, Nb, Ba and Au, *Nucl. Instr. Methods. Phys. Res. B* **129** (1997) 153–193.
- [2.34] DMITRIEV, P.P., Radionuclide yield in reactions with protons, deuterons, alpha particles and helium-3 (Handbook), *Energoatomizdat, Moscow* (1986).
- [2.35] INTERNATIONAL ATOMIC ENERGY AGENCY, Charged Particle Cross-section Database for Medical Radioisotope Production: Diagnostic Radioisotopes and Monitor Reactions, IAEA-TECDOC-1211, IAEA, Vienna (2001).
- [2.36] GANDARIAS-CRUZ, D., OKAMOTO, K., Status of the Compilation of Nuclear Data for Medical Radioisotopes Produced by Accelerators, Rep. INDC(NDS)-209/GZ, International Atomic Energy Agency, Vienna (1988).
- [2.37] HORIGUCHI, H., KUMAHORA, H., INOUE, H., YOSHIZAWA, Y., Excitation function of $\text{Ge}(p, xnyp)$ reactions and production of ^{68}Ge , *Int. J. Appl. Radiat. Isot.* **34** (1982) 1531–1535.
- [2.38] MAUSNER, L.F., Brookhaven National Laboratory, USA, personal communication (2007).
- [2.39] PETERSON, E.J., Accelerator radioisotopes save lives: The isotope production facility at Los Alamos, *Los Alamos Science* **30** (2006), <http://library.lanl.gov/cgi-bin/getfile?30-14.pdf>

- [2.40] PHILLIPS, D.R., Radioisotope Production at Los Alamos National Laboratory, presented at Specialization School on Health Physics, Milan, 2002, <http://www.mi.infn.it/conferences/phillips/Lanl.pdf>
- [2.41] VAN DER WALT, T.N., VERMEULEN, C., Thick targets for the production of some radionuclides and the chemical processing of these targets at iThemba LABS, Nucl. Instr. Methods Phys. Res. A **521** (2004) 171–175.
- [2.42] FASSBENDER, M., et al., Nuclear chemical aspects of medical generator nuclide production at the Los Alamos hot cell facility, Radiochim. Acta **92** (2004) 237–243.
- [2.43] FASSBENDER, M., et al., Proton beam simulation with MCNPX: Gallium metal activation estimates below 30 MeV relevant to the bulk production of ^{68}Ge and ^{65}Zn , Nucl. Instr. Methods Phys. Res. B **261** (2007) 742–746.
- [2.44] ARZUMANOV, A.A., ALEXANDRENKO, V.V., BORISENKO, A.R., IGNATENKO, D.N., KOPTEV, V.K., “Technique for irradiation of Nb-Ga targets at Kazakhstan isochronous cyclotron”, in Proc. 17th Int. Conf. on Cyclotrons and Their Applications, Tokyo, 2004, CERN, Geneva (2004), http://epaper.kek.jp/c04/data/CYC2004_papers/19P06.pdf
- [2.45] ESIN, K., et al., Isotope Production for Medical and Technical Use at Moscow Meson Factory LINAC, CERN, Geneva (2006), <http://accelconf.web.cern.ch/accelconf/196/PAPERS/MOP61.PDF>
- [2.46] LOC'H, C., MAZIÈRE, B., COMAR, D., KNIPPER, R., A new preparation of germanium 68, Int. J. Appl. Radiat. Isot. **33** (1982) 267–270.
- [2.47] NAIDOO, C., VAN DER WALT, T.N., RAUBENHEIMER, H.G., Cyclotron production of ^{68}Ge with a Ga_2O target, Int. J. Radioanal. Nucl. Chem. **253** (2002) 221–225.
- [2.48] GLEASON, G.I., A positron cow, Int. J. Appl. Radiat. Isot. **8** (1960) 90–94.
- [2.49] PAO, P.J., SILVESTER, D.J., WATERS, S.L., A new method for the preparation of ^{68}Ga -generators following proton bombardment of gallium oxide targets, J. Radioanal. Nucl. Chem. **64** (1981) 267–272.
- [2.50] FASSBENDER, M., JAMRISKA, D.J., HAMILTON, V.T., NORTIER, F.M., PHILLIPS, D.R., Radiopharmaceutical studies and nuclear medicine: Simultaneous ^{68}Ge and ^{88}Zr recovery from proton irradiated Ga/Nb capsules (LA-UR #03-2319), Int. J. Radioanal. Nucl. Chem. **263** (2005) 497–502.
- [2.51] MEYER, G.-J., MÄCKE, H.R., SCHUHMACHER, J., KNAPP, W.H., HOFMANN, M., ^{68}Ga -labelled DOTA-derivatised peptide ligands, Eur. J. Nucl. Med. **31** (2004) 1097–1104.
- [2.52] VELIKYAN, I., BEYER, G.J., LÄNGSTRÖM, B., Microwave-supported preparation of ^{68}Ga bioconjugates with high specific radioactivity, Bioconj. Chem. **15** (2004) 554–560.
- [2.53] BREEMAN, W.A.P., et al., Radiolabelling DOTA-peptides with ^{68}Ga , Eur. J. Nucl. Med. **32** (2004) 478–485.
- [2.54] ZHERNOSEKOV, K.P., et al., Processing of generator produced ^{68}Ga for medical application, J. Nucl. Med. **48** (2007) 1741–1748.
- [2.55] MEYER, G.-J., GIELOW, P., BÖRNER, A.R., HOFMANN, M., KNAPP, W.H., Ga-67 and Ga-68 labelled DOTA-derivatised peptide-ligands, Nuklearmedizin **6** (2005) A192.
- [2.56] DECRISTOFORO, C., et al., Radiolabelling of DOTA-derivatised peptides with ^{68}Ga via a direct approach: Optimization and routine clinical application, Nuklearmedizin **6** (2005) A191.

Chapter 3

PRODUCTION AND PROCESSING OF ^{82}Sr

K.D. JOHN

Los Alamos National Laboratory,
Los Alamos, California,
United States of America

L. MAUSNER

Brookhaven National Laboratory,
Upton, New York,
United States of America

T.J. RUTH

TRIUMF,
Vancouver, Canada

3.1. INTRODUCTION

Evaluation of cardiac viability by radionuclide imaging is one of the most powerful means available for ascertaining whether bypass surgery should be performed to restore blood flow following an infarction. Typically this test involves two PET scans: a blood flow scan to determine the areas of the myocardium where there is a lack of perfusion and an ^{18}F -fluorodeoxyglucose (FDG) scan to indicate the metabolic capacity of the myocardium. The normoxic heart tissue typically uses fatty acids for metabolic energy. However, in an anaerobic environment the tissue will consume glucose, because it contains sufficient oxygen within the molecule to metabolize the glucose. Thus the combined tests are aimed at showing a match or mismatch between the pair of scans. A match indicates an area of the heart where the lack of perfusion equals the area without metabolic activity, suggesting that the tissue is no longer viable and would not benefit from reperfusion. In the event of a mismatch (where there is a lack of blood flow but where the same area demonstrates a capacity for metabolism by FDG uptake), the tissue in question might respond favourably to the provision of a new source of blood through bypass surgery. In numerous studies using this technique it has been demonstrated that unnecessary surgeries can be avoided, thus reducing morbidity and health care costs. There are a number of candidate isotopes that can be used for monitoring cardiac blood flow, including ^{82}Rb , an analogue of potassium formed by the decay of ^{82}Sr . This

chapter describes the production and processing of the radioactive isotope ^{82}Sr to be used as a parent radionuclide for the production of $^{82}\text{Sr}/^{82}\text{Rb}$ generators.

3.2. BACKGROUND

Measurement of blood flow has been one of the most common uses of PET. The tracer H_2^{15}O began to be used in the mid-1960s and became the most widely used tracer in the 1970s and early 1980s. The interest in using PET to evaluate cardiac viability led to the increased use of potassium ion analogues for assessing blood flow. Table 3.1 provides a list of the physiological and physical properties of the radiotracers that have been used for evaluating myocardial blood flow.

In the late 1980s, ^{82}Rb became the tracer of choice for assessing cardiac blood flow, especially at those centres without access to an in-house accelerator that would allow production of $^{13}\text{NH}_3$. In 1987, a special issue of the International Journal of Radiation Applications and Instrumentation [3.5] was devoted to the production and use of the $^{82}\text{Sr}/^{82}\text{Rb}$ generator. While demand for ^{82}Rb was expected to grow owing to the clinical information available from its use, the monthly cost of acquiring the $^{82}\text{Sr}/^{82}\text{Rb}$ generator (approximately US \$25 000), in addition to the initial investment needed for the elution/infusion device, was considered prohibitive. Nevertheless, the $^{82}\text{Sr}/^{82}\text{Rb}$ generator is currently being used by approximately 60 sites worldwide, and its use appears to have increased in recent years (2006–2008). The cost of ^{82}Sr production is relatively high, because it can only be produced via high energy protons at accelerators available within national laboratories in Canada, the Russian Federation, South Africa and the USA. Scheduling production irradiations is a challenge, since most of the facilities involved in the production of the parent radionuclide (^{82}Sr) have other missions and are not available for production throughout the calendar year.

3.3. NUCLEAR DECAY CHARACTERISTICS

Strontium-82 ($T_{1/2}$: 25.5 d, EC: 100%) is primarily used to generate the PET diagnostic radioisotope ^{82g}Rb ($T_{1/2}$: 1.3 min, photons 511 keV 191%, 776.5 keV 15.1%), which has been used in myocardial perfusion studies (see the ‘Applications’ section of the bibliography at the end of this chapter). The short half-life of ^{82}Rb allows scans to be performed sequentially every 10 min, while minimizing the radiation dose to the patient. Furthermore, ^{82}Rb has also been employed in renal and blood vessel disease studies [3.4, 3.6]. A detailed paper has been published on the Cardiogen PET generator project of the US Department of Energy (DOE) [3.7].

TABLE 3.1. EXAMPLES OF MYOCARDIAL BLOOD FLOW TRACERS FOR PET

Tracer	$T_{1/2}$ (min)	β^+ (%)	β^+ range (mm)	Production routes	Reference
$H_2^{15}O$	2.03	99.9	1.02	$^{14}N(d,n)$ $^{15}N(p,n)$	[3.1]
$^{13}NH_3$	9.97	99.8	0.57	$^{16}O(p,\alpha)$	[3.2]
^{38}K	7.6	100	2.0	$^{40}Ar(p,3n)$	[3.3]
^{82}Rb	1.27	100	2.60	^{82}Sr generator	[3.4]

3.4. PRODUCTION PROCESSES

3.4.1. Nuclear reactions

Strontium-82 has been produced via several different reaction routes (see Table 3.2). The earliest routes used high energy spallation reactions, in particular with Mo metal as the target. It is also possible to irradiate natural Yt targets at high energy; however, the measured cross-sections are rather low, and this method has not been pursued [3.8]. High energy 3He and alpha particle irradiation of natural Kr have also been investigated, but yields are low and there are very few accelerators in operation capable of accelerating He ions to the energies required. In the late 1970s, investigations began into the use of the $^{85}Rb(p,4n)$ or $^{nat}Rb(p,xn)$ reactions with a natural RbCl target material, and this remains the principal production technique. Several groups have also investigated the use of natural abundance Rb metal target material. Each method represents different challenges for targetry, process chemistry, practical yield, radionuclidic purity and availability.

The high energy of the few accelerator facilities capable of using the spallation route (e.g. Los Alamos Meson Physics Facility (LAMPF), Tri-University Meson Facility (TRIUMF)) allowed very thick targets of hundreds of grams to be irradiated, resulting in substantial production yields. The combination of a massive Mo metal target and high beam intensity overcame the intrinsically low reaction cross-section (23 mb at 800 MeV) [3.9]. With the high proton energy and intensity (up to 1000 μA at 800 MeV) available for isotope production at the LAMPF (now the Los Alamos Neutron Science Center (LANSCE)), it was possible to achieve batch amounts of as much as 740 GBq (20 Ci) in a bombardment lasting several weeks, with a typical yield of 3.7 MBq/ μAh [3.7, 3.10, 3.11]. The 400–500 g target was robust because of the

TABLE 3.2. NUCLEAR REACTION ROUTES FOR PRODUCTION OF ^{82}Sr

Reaction	Target material	Projectile energy (MeV)
Y(p, spallation)	Yttrium oxide	60–240
Mo(p,spallation)	Molybdenum metal	500–700
Rb(p,xn)	RbCl or Rb metal	40–90
Kr(α ,pxn)	Kr gas	20–120
Kr(^3He ,xn)	Kr gas	20–90

good thermal conductivity of the Mo metal discs and the ability to use very thick stainless steel cladding windows, since energy loss in the windows was not a serious concern with the high proton energy available. Also, this irradiation co-produced another useful isotope, ^{77}Br . A yield of 1.5 MBq/ μAh at 500 MeV has been reported using a somewhat smaller Mo pressed pellet target [3.12].

Another possible method for producing ^{82}Sr is by ^3He or alpha particle irradiation of Kr gas by the $^{\text{nat}}\text{Kr}(^3\text{He},\text{xn})^{82}\text{Sr}$ and $^{\text{nat}}\text{Kr}(\alpha,\text{xn})^{82}\text{Sr}$ reactions. These approaches have been investigated as well [3.13, 3.14]. Nuclear excitation functions from 20–90 MeV ^3He and 20–120 MeV alpha irradiations were measured on a series of gas cells filled with natural Kr to a pressure of 1–3 bar². As is now typical for gas targets, a conical shape was used to take account of lateral spread as the beam penetrates the gas, thus preventing the beam from hitting the walls. This concept minimizes the need to cool the chamber walls and reduces activation of the target chamber. With ^3He particles, the ^{82}Sr production begins at approximately 18 MeV and increases to a maximum of 80 mb at 62 MeV. The cross-sections for ^{83}Sr exceed those of ^{82}Sr for all energies below 55 MeV and are approximately equal to them up to 90 MeV. The cross-sections of ^{85}Sr exceed those of ^{82}Sr for all energies below 45 MeV, but fall to about 20% of the ^{82}Sr cross-sections at 90 MeV. Therefore the amounts of $^{83,85}\text{Sr}$ co-produced with ^{82}Sr are large, and there is no energy range that allows pure ^{82}Sr production alone.

3.4.2. Thick target yields

Thick target yields were calculated from the measured cross-sections. For energies up to 55 MeV, the ^{85}Sr yield is higher than the ^{82}Sr yield, but the ratio is reversed beyond 55 MeV. At all energies, the ^{83}Sr yield is highest; however,

² 1 bar = 10^5 Pa.

owing to its shorter half-life, after several weeks of decay ^{83}Sr would become minimal. However, since the ^{83}Sr to ^{82}Sr ratio is higher from this nuclear reaction than from the other production modes, the decay period would need to be longer and the deliverable quantity of ^{82}Sr would thus be reduced. Irradiation times longer than three days would help reduce the ^{83}Sr to ^{82}Sr ratio, since production of ^{83}Sr would begin to saturate. The calculated thick target yield at EOB from 90–20 MeV was 1290 kBq/ μAh . At low beam intensities (up to 3 μA), the experimental yields were close to the values calculated from the excitation function. However, at 15 μA the EOB production yield decreased by 50% to 630 kBq/ μAh , due to gas density reduction in the beam strike area (even though overall gas pressure increased to 7 bar during irradiation). The ^{85}Sr to ^{82}Sr ratio calculated for a short (50 h) irradiation is better than that from the spallation route, but would be higher in a longer irradiation used for practical production.

The cross-sections for ^{82}Sr are all smaller with the alpha induced reaction on Kr than with ^3He irradiation, and the cross-sections for $^{83,85}\text{Sr}$ impurities are higher. Thick target yield from 120–20 MeV was calculated from these data to be 1920 kBq/ μAh , but experimentally was measured to be only 960 kBq/ μAh . With alpha irradiation, the yield of ^{85}Sr is higher than that of ^{82}Sr at all energies. For the same incident energy there is more ^{82}Sr production with the ^3He route. The calculated ^{85}Sr to ^{82}Sr ratio for a short (50 h) irradiation is similar to that from the spallation route, but would worsen over a lengthy production run. Alpha irradiation may be the more practical route compared with ^3He irradiation, because of the greater availability of high energy alpha sources and the convenience of not needing to recover normal He gas, as is necessary with ^3He . It would be possible to approximately double the yield of ^{82}Sr with either of these reactions if enriched ^{84}Kr were used as the target material, but at an increased cost. Nevertheless, the long irradiations required, the relatively low atom density of the target and the relatively low beam current available with ^3He and alpha beams compared with proton accelerators make these methods uneconomical compared with the solid Mo or Rb based targets.

By far the most thoroughly investigated and widely used method for producing ^{82}Sr is the $^{\text{nat}}\text{Rb}(p,xn)$ reaction. The first systematic effort to measure the excitation function used enriched $^{85}\text{RbCl}$ powder mixed with Al powder and spread to a 50 μm thickness on Mylar film [3.15]. This work measured a peak ^{82}Sr cross-section of approximately 200 mb at 50 MeV and 400 mb at 36 MeV for ^{83}Sr . The production of ^{85}Sr was not measured. Measured thick target yield (67–49 MeV) on a RbCl pellet (2.75 mg/cm²) at low beam current and short irradiation was close to the theoretical value calculated from this excitation function but fell off significantly with higher integrated beam current [3.16].

Several other groups have measured the excitation function using the well known thin stacked target technique on both natural RbCl [3.17–3.22] and

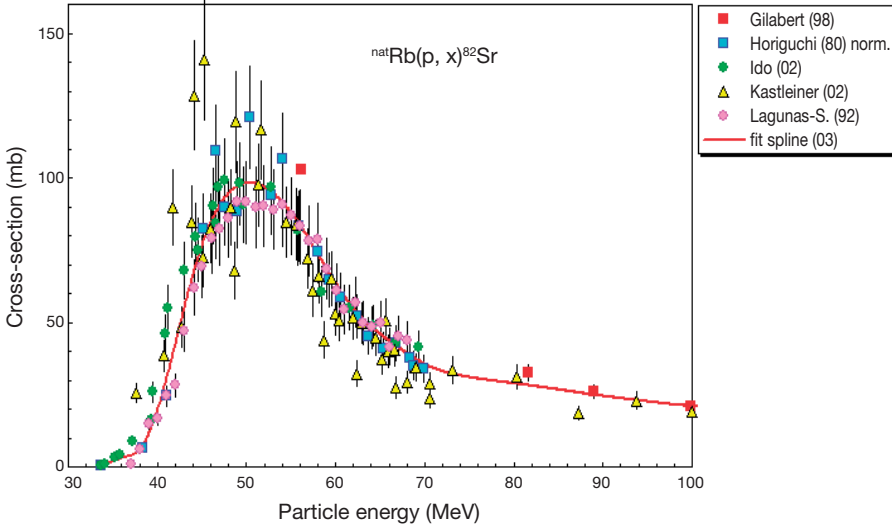


FIG. 3.1. Excitation function for the production of ^{82}Sr from natural Rb (source: IAEA [3.21]).

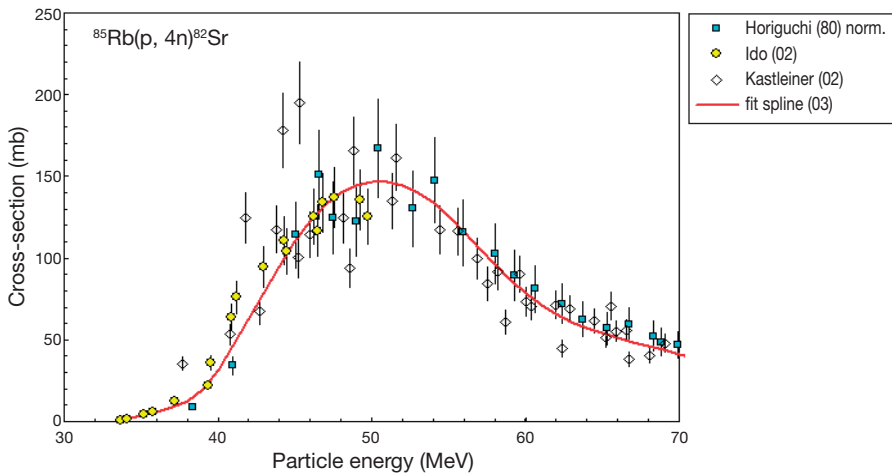


FIG. 3.2. Excitation function for the production of ^{82}Sr from enriched ^{85}Rb (source: IAEA [3.21]).

enriched $^{85}\text{RbCl}$ (see Figs 3.1 and 3.2) [3.23]. The peak cross-section measured by Zaitseva et al. [3.18] using relatively thick RbCl pressed pellets and 100 MeV incident proton energy was 180 mb at 52 MeV for natural RbCl, which is in reasonable agreement with the findings of Horiguchi et al. [3.15]. However, Lagunas-Solar measured cross-sections with a broad maximum at 90 mb extending from 48 to 54 MeV [3.17]. The details of the RbCl target and

measurement method were not given. This result was half the previous measurements. Ido et al. [3.19] used thin pressed pellets (~ 100 mg/cm²) of RbCl, but the density was not stated and thus there could be some uncertainty of the energy loss calculations. The cross-section measurements of Ido et al. showed a maximum of 96–99 mb from 47–52 MeV, which is in good agreement both in excitation function shape and quantity with the results of Lagunas-Solar [3.17]. The findings of Buthelezei et al. [3.20] showed good agreement with those of Horiguchi et al. [3.15] and Deptula et al. [3.22] only for incident energies below 45 MeV and above 62 MeV, but with a peak cross-section that was much lower at 123 mb and shifted to slightly lower energy at 50 MeV.

To address these substantial differences, several groups attempted to again measure the excitation function. Kastleiner et al. [3.23] took great care to use a special sedimentation method to prepare uniform and very thin (5–10 mg/cm²) RbCl targets. A comparison of the ^{nat}Rb(p,xn)⁸²Sr experimental excitation function in the literature [3.21] with ALICE IPPE modelling results revealed that the model overestimates the empirical values by factors of 1.6–2.0.

3.4.3. Comparison of production methods by different suppliers

For the production of ⁸²Sr within the US DOE Medical Radioisotope Program, Rb metal or RbCl targets are irradiated at BNL and LANL, and are also provided from production facilities from around the world. Table 3.3 provides the reaction conditions for the various suppliers of the ⁸²Sr.

The batch yields from the different production facilities are difficult to compare because of the various conditions under which the ⁸²Sr is prepared, including, for example, the beam flux and length of bombardment parameters, which are not standardized.

3.4.4. Targetry

The RbCl target material is readily available at a high level of purity, is easy to dissolve in water, and can be pressed into a pellet at near theoretical density (2.76 g/cm³), or melted and cast into an appropriate shape for irradiation. Interestingly, the Rb atom density is higher in RbCl than in the pure metal, so the presence of the chloride atom does not decrease yield compared with the pure metal. Moreover, target fabrication is simpler and safer with RbCl than with Rb metal. Rubidium metal can ignite in the presence of air or moisture, so handling in a dry inert atmosphere is required for both target fabrication and target opening. This safety issue is more pressing after irradiation. The RbCl is also much less corrosive to the claddings than is molten Rb metal. Although stainless steel target cladding is often used, Inconel is preferred by the BNL and LANL

TABLE 3.3. IRRADIATION CONDITIONS AND YIELDS FROM THE CURRENT SUPPLIERS OF ^{82}Sr

Laboratory	Target	Irradiation conditions	Yields (EOB, MBq/ μAh) ^a
Brookhaven National Laboratory	RbCl	2 targets (96–74 and 66–44 MeV), 14 d irradiation	10.5
Institute for Nuclear Research, Moscow	Rb metal	100–40 MeV	18
Los Alamos National Laboratory	RbCl	2 targets (97–71 and 65–45 MeV)	13.3 8.2
iThemba Laboratories/NAC	RbCl	61–44 MeV	8.6

^aBatch sizes typically range from approximately 65 to 450 GBq.

groups. Chemical processing of RbCl is faster, simpler and much safer than chemical processing of a Rb metal target (see Section 3.5), because of the need to use anhydrous reagents and an inert atmosphere at the beginning of Rb processing. In addition, relatively large quantities of Fe must be removed in the separation, because the Rb is corrosive to the vessel walls.

The good thermal conductivity of the Rb metal ($58.2 \text{ W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$) permits use of very thick targets (up to 7 cm) [3.24], leading to substantial batch quantities. In contrast, the thermal conductivity of RbCl is low ($7.6 \text{ W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$), so that it is difficult to cool a thick target. A related issue is that there can be a large temperature difference between the target interior and the cooled outside surfaces. Indeed, if the RbCl melts in the target centre from the energy deposited by the proton beam, the material near to the cooled surfaces may remain solid. Since RbCl expands by 19% upon melting, the molten material may then push outward from the central hot spot and cause a thinning of the target in this area. This may reduce the yield to some extent. Considerable effort has gone into target design to minimize such effects. The beam intensity profile and pulse structure, if any, also affect the target thermal behaviour. A uniform intensity profile is best but is difficult to achieve in practice. The very large pulsed power that is delivered by the linear energy accelerators (LINACs) can be a problem. However, the relatively large size of the RbCl targets (>30 g) and their low thermal conductivity mean that the thermal time constant is long; that is, the targets do not heat up and cool down very much during and between pulses, but the temperature oscillates a little about a mean. Targets with good thermal conductivity can experience very large temperature swings in a pulsed beam.

3.5. CHEMICAL ASPECTS

Cautionary note: It should be noted that metallic Rb is very reactive and releases hydrogen when reacted with water. The following web site illustrates the hazard associated with alkali metals and water: http://www.metacafe.com/watch/178735/alkali_metals_and_water/

The chemical processing of the irradiated targets varies according to the target material. There are essentially two target materials and thus two different chemical processes. The LANL Hot Cell Facility and the Target Processing Laboratory at BNL regularly process bulk amounts of ^{82}Sr , mainly for medical applications. Irradiated targets are shipped to BNL or LANL for chemical processing. Radiochemical separation methods based on liquid-liquid extraction and ion exchange have been specifically developed or modified to suit remote control operations in a hot cell. Product radioisotope preparations meet the requirements of the US Food and Drug Administration for pharmaceutical precursors.

Overall experimental yields generally correspond to more than 80% of the theoretical thick target yields calculated on the basis of reaction cross-section data. A comparison of experimental reaction cross-sections with ALICE IPPE model calculation results confirms that the underlying model describes nuclear processes on medium-mass target nuclei in a satisfactory manner, while giving poor results for heavier target elements. Radionuclide shipments of about 100 GBq occur biweekly.

The goal of the chemical processing at BNL and LANL is to prepare $^{82}\text{SrCl}_2$ with a high specific activity and a minimum concentration of 2.22 GBq (60 mCi)/mL, dissolved in a slightly acidic aqueous matrix (typically 0.1 mol/L HCl), which is subsequently shipped to the generator manufacturer. The $^{82}\text{Sr}/^{82}\text{Rb}$ radionuclide generator principle is based on inorganic cation exchange on hydrous tin oxide ($\text{SnO}_2 \cdot x\text{H}_2\text{O}$, where $x = 1, 2$). A more detailed description of $^{82}\text{Sr}/^{82}\text{Rb}$ generator manufacturing is given in Ref. [3.25].

Owing to its extremely high chemical reactivity, Rb metal (typically in the amount of 20 g per target) cannot be immediately hydrolysed with water. Instead, the target containing the alkaline metal is dissolved in a higher alcohol (typically propan-2-ol) under argon atmosphere at a controllable rate (for details, see Refs [3.6, 3.24, 3.26]). The resulting rubidium alcoholate, in turn, is decomposed by the addition of aqueous HCl, and the resultant RbCl solution is evaporated to dryness. To remove Fe impurities originating from the target capsule, the dry residue is re-dissolved in acidified water, and Fe^{2+} is oxidized to Fe^{3+} with H_2O_2 . Next, HCl (12 mol/L) is added to obtain optimal Fe^{3+} resin sorption. The solution is passed through an AG 1-X8 anion exchanger, where FeCl_6^{3-} is retained while $\text{Sr}^{2+}/\text{Rb}^+$ is eluted. The residual feed solution is then washed off the column with

additional HCl (6 mol/L). The combined eluates are evaporated to dryness, and the RbCl residue is re-dissolved in a $\text{NH}_4^+/\text{NH}_3$ buffer solution at pH9–10.

In the case of RbCl targets, at both BNL and LANL the processing starts at this point, after the exterior of the target capsules is washed with acid. The irradiated RbCl cake is then dissolved in water. With both Rb metal and RbCl targets, the buffered RbCl solution is filtered and then transferred onto a column containing equilibrated Chelex 100 (chelating) cation exchange resin, whereby the actual Sr/Rb separation is achieved: bivalent $^{82}\text{Sr}^{2+}$ is chelated and retained on the column at a high pH, while Rb^+ is eluted. The column is washed with additional buffer solution to remove as much Rb^+ as possible. Subsequently, $^{82}\text{Sr}^{2+}$ is desorbed from the column with HCl (6 mol/L), and evaporated to dryness.

Further purification (i.e. from Rb, ^{75}Se and ^7Be traces, and buffer solids) is accomplished with an additional cation exchange step: the dry residue containing $^{82}\text{Sr}^{2+}$ is taken up with HCl (0.1 mol/L) and loaded onto the cation exchange column (AG 50W-X8). The column is carefully washed with an HCl gradient (range: 0.1–1 mol/L) to remove Rb traces. This step is monitored via gamma ray spectrometry. The product is subsequently desorbed with HCl (4 mol/L). If desired at this point, further reduction of Fe can be achieved by anion exchange with AG 1X in 6 mol/L. The Sr has no retention, and the solution is collected and evaporated. Resin breakdown residues as well as NH_4^+ traces are removed with two evaporation steps using concentrated HNO_3 . Treatment with HCl (6 mol/L) and evaporation converts the activity back to the chloride form, which is dissolved in HCl (0.1 mol/L) to yield a pure product consistent with pharmaceutical requirements.

Strontium-85 is the most important contaminant in the production of ^{82}Sr and has a half-life of 64.8 d. The (p,xn) reaction on natural Rb produces approximately 40% as much ^{82}Sr over the energy range of 50–60 MeV at EOB. The ratio of ^{85}Sr to ^{82}Sr must not exceed 5.0 if the generators are intended for human use. The ^{82}Sr content present initially limits the shelf life of the $^{82}\text{Sr}/^{82}\text{Rb}$ generator. Thus the shelf life of ^{82}Sr produced using natural Rb targets is several weeks if not months, depending on the quantity of ^{82}Sr produced.

Because the characteristic gamma ray for ^{85}Sr is so close to the annihilation photon energy (514 versus 511 keV), care must be exercised in determining the amount of ^{85}Sr contamination. It has been noted that the various software packages for analysing gamma ray spectra give differing results when deconvoluting 514 keV photons from annihilation radiation. Typical gamma ray spectra are shown in Figs 3.3 and 3.4. Figure 3.3 shows the full energy spectra up to approximately 3.5 MeV, whereas Fig. 3.4 shows an enlarged view of the 511 keV region.

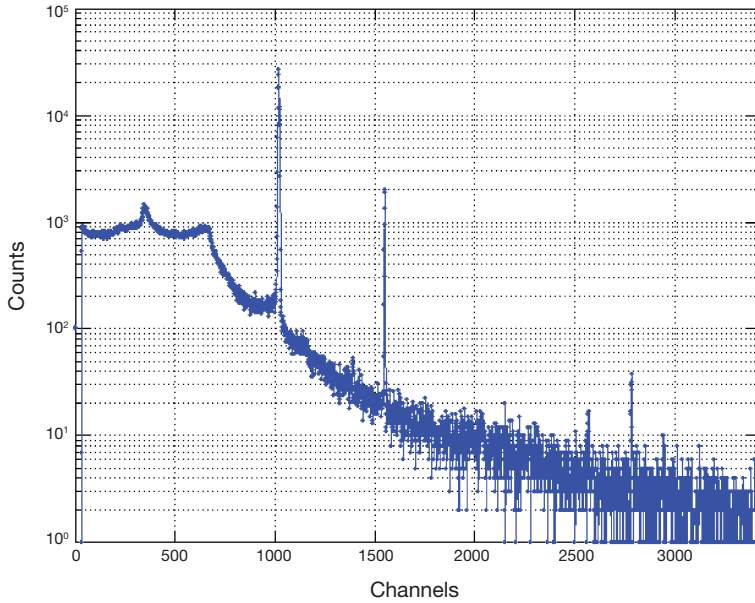


FIG. 3.3. Measured pulse height gamma spectra of a $^{82}\text{Sr}/^{85}\text{Sr}$ sample, 0–3500 keV. Each channel equals 0.5 keV.

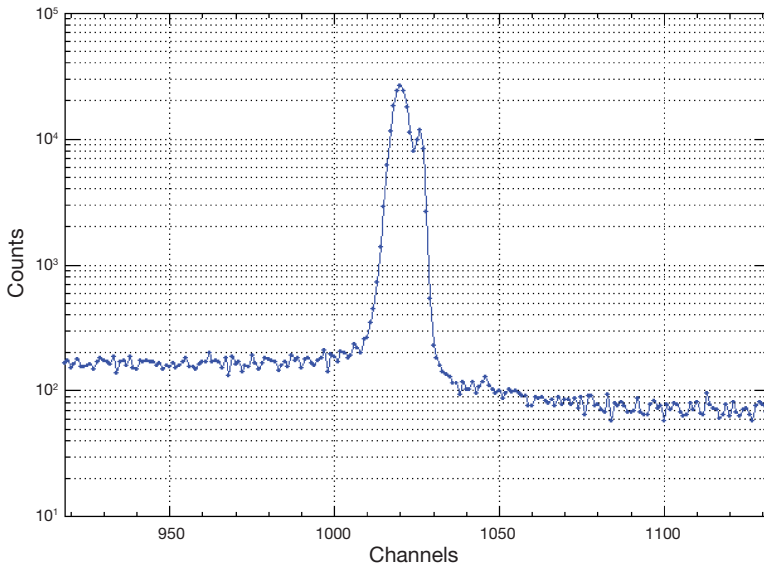


FIG. 3.4. Measured pulse height gamma spectra of the previous $^{82}\text{Sr}/^{85}\text{Sr}$ sample enlarged to show the small separation of the positron at 511 keV and the ^{85}Sr gamma. Each channel equals 0.5 keV.

3.6. CONCLUSION

Rubidium-82 has been shown to be of great value for the clinical assessment of myocardial blood flow. Its availability via the $^{82}\text{Sr}/^{82}\text{Rb}$ generator makes it potentially useful for any PET site interested in cardiac studies, even those sites without a cyclotron. For more than a decade, the number of generator users remained rather constant throughout the world. However, recently (2006–2008) there have been indications of growing interest in the use of this system. Unfortunately, the parent radionuclide (^{82}Sr) can only be produced efficiently with a high energy cyclotron (~70 MeV). The target material is either RbCl or Rb metal.

While the Rb metal target has better thermal conductivity and thus can be operated at higher beam currents, there is the ever present safety concern about the possibility of the Rb, an alkali metal, coming into contact with water, resulting in a violent chemical reaction and leading to hydrogen release and possible explosion. Nevertheless, Rb metal targets have been operated for extended periods with no major problems.

Because of the limited number of facilities capable of producing the ^{82}Sr parent, growth in the use of ^{82}Rb may remain somewhat limited. If and when the production of ^{82}Sr becomes economically competitive with alternative probes, the use of this important generator system can be expected to increase.

REFERENCES TO CHAPTER 3

- [3.1] ADACHI, I., et al., Assessment of myocardial perfusion by dynamic O-15-labeled water PET imaging: Validation of a new fast factor analysis, *J. Nucl. Cardiol.* **14** (2007) 698–705.
- [3.2] HICKEY, K.T., et al., An improved model for the measurement of myocardial perfusion in human beings using N-13 ammonia, *J. Nucl. Cardiol.* **12** (2005) 311–317.
- [3.3] MELON, P.G., et al., Myocardial kinetics of potassium-38 in humans and comparison with copper-62-PTSM, *J. Nucl. Med.* **35** (1994) 1116–1122.
- [3.4] DOU, Y., et al., Rb-82 positron emission tomography identifies left main or three vessel coronary disease, *J. Nucl. Med.* **43** Suppl. (2002) 175P.
- [3.5] *International Journal of Radiation Applications and Instrumentation. Part A: Applied Radiation and Isotopes*, **38** 3 (1987) 171–239.
- [3.6] PRETORIUS, P.H., FUNG, L.T., SCHELL, C.P., KING, M.A., Measurement of effective functional renal volume of small kidneys using Rb-82 and a hybrid gamma camera, *J. Nucl. Med.* **43** Suppl. (2002) 352P.
- [3.7] PHILLIPS, D.R., et al., Production of strontium-82 for the Cardiogen (R) PET generator: A project of the Department of Energy Virtual Isotope Center, *Radiochim. Acta* **88** (2000) 149–155.

- [3.8] CARETTO, A.A., Jr., WIIG, E.O., Interaction of yttrium with protons of energy between 60 and 240 MeV, *Phys. Rev.* **115** (1959) 1238–1242.
- [3.9] GRANT, P.M., ERDAL, B.R., O'BRIEN, H.A., Jr., Medium energy spallation cross sections, 2. Mo irradiation with 800 MeV protons, *Appl. Radiat. Isot.* **34** (1983) 1631–1632.
- [3.10] THOMAS, K.E., Isotope production from molybdenum targets, *Radiochim. Acta* **37** (1984) 37–141.
- [3.11] THOMAS, K.E., ^{82}Sr production at Los Alamos National Laboratory, *Appl. Radiat. Isot.* **38** (1987) 175.
- [3.12] ROBERTSON, R., GRAHAM, D., TREVANA, I.C., Radioisotope production via 500 MeV proton induced reactions, *J. Labelled Compd. Radiopharm.* **19** (1982) 1368.
- [3.13] TARKANYI, F., QAIM, S.M., STOECKLIN, G., Excitation-functions of He-3-particle and alpha-particle induced nuclear-reactions on natural krypton: Production of Sr-82 at a compact cyclotron, *Appl. Radiat. Isot.* **39** (1988) 135–143.
- [3.14] TARKANYI, F., QAIM, S.M., STOECKLIN, G., Excitation-functions of He-3-particle and alpha-particle induced nuclear-reactions on natural krypton with special reference to the production of Sr-82, *Appl. Radiat. Isot., A* **41** (1990) 91.
- [3.15] HORIGUCHI, T., et al., Excitation functions of proton induced nuclear reactions on ^{85}Rb , *Appl. Radiat. Isot.* **31** (1980) 141–151.
- [3.16] HUSZAR, I., et al., “The development of a production process for Sr-82”, *Proc. 7th Int. Symp. on Radiopharmaceutical Chemistry, Groningen, 1988.*
- [3.17] LAGUNAS-SOLAR, M., Radionuclide production with >70 MeV proton accelerators: Current and future prospects, *Nucl. Instrum. Methods B* **69** (1992) 452–462.
- [3.18] ZAITSEVA, N.G., et al., Cross-sections for the 100 MeV proton-induced nuclear reactions and yields of some radionuclides used in nuclear medicine, *Radiochim. Acta* **54** (1991) 57.
- [3.19] IDO, T., et al., Excitation functions of proton induced nuclear reactions on Rb-nat from 30 to 70 MeV. Implication for the production of Sr-82 and other medically important Rb and Sr radioisotopes, *Nucl. Instrum. Methods Phys. Res. B* **194** (2002) 369–388.
- [3.20] BUTHELEZEI, E.Z., NORTIER, F.M., SCHROEDER, I.W., Excitation functions for the production of Sr-82 by proton bombardment of ^{nat}Rb at energies up to 100 MeV, *Appl. Radiat. Isot.* **64** (2006) 915–924.
- [3.21] QAIM, S.M., et al., Charged-particle Cross Section Database for Medical Radioisotope Production, International Atomic Energy Agency, Vienna (2001), <http://www-nds.iaea.org/medical/>
- [3.22] DEPTULA, C., et al., Excitation functions and yields for medically important generators ^{82}Sr - ^{82}Rb , ^{123}Xe - ^{123}I and ^{201}Bi - ^{201}Pb - ^{201}Tl obtained with 100 MeV protons, *Nukleonika* **35** (1990) 3–22.
- [3.23] KASTLEINER, S., et al., Excitation functions of $^{85}\text{Rb}(p,xn)^{85m,g,83,82,81}\text{Sr}$ reactions up to 100 MeV: Integral tests of cross section data, comparison of production routes of ^{83}Sr and thick target yield of ^{82}Sr , *Appl. Radiat. Isot.* **56** (2002) 685.
- [3.24] ZHUIKOV, B.L., KOKHANYUK, V.M., KONYAKHIN, N.A., Target irradiation facility and targetry development at the 160 MeV proton beam of Moscow LINAC, *Nucl. Instrum. Meth. Phys. Res. A* **438** (1999) 173–179.

- [3.25] ALVAREZ-DIEZ, T.M., DEKEMP, R., BEANLANDS, R., VINCENT, J., Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography, *Appl. Radiat. Isot.* **50** (1999) 1015–1023.
- [3.26] CACKETTE, M.R., RUTH, T.J., VINCENT, J.S., Sr-82 production from metallic Rb targets and development of an Rb-82 generator system, *Appl. Radiat. Isot.* **44** (1993) 917–922.

BIBLIOGRAPHY

Background

- BUDINGER, T.F., YANO, Y., HOOP, B., Comparison of Rb-82⁺ and ¹³NH₃ for myocardial positron scintigraphy, *J. Nucl. Med.* **16** (1975) 429–431.
- BURNS, R.J., Rb-82 PET — Essential or not, *J. Nucl. Med.* **34** (1993) 1834.
- GRANT, P.M., ERDAL, B.R., O'BRIEN, H.A., Sr-82-Rb-82 isotope generator for use in Nuclear-Medicine, *J. Nucl. Med.* **16** (1975) 300–304.
- GUILLAUME, M., BRIHAYE, C., Generators of ultra-short lived radionuclides for routine clinical-applications, *Radiochim. Acta* **41** (1987) 119–130.
- JONES, T., Clinical uses of Sr-82/Rb-82 generators, *Appl. Radiat. Isot.* **38** (1987) 171–173.
- KENSETT, M.J., et al., Experience with a Sr-82/Rb-82 generator for clinical use, *Appl. Radiat. Isot.* **38** (1987) 227–231.
- KRIZEK, H., et al., Generator production of Rb-82 for clinical use, *J. Nucl. Med.* **18** (1977) 609.
- MacINTYRE, W.J., et al., Rb-82 PET-Essential or not – Reply, *J. Nucl. Med.* **34** (1993) 1834.
- SCHLEIPMAN, A.R., et al., Occupational radiation dose associated with Rb-82 myocardial perfusion positron emission tomography imaging, *J. Nucl. Cardiol.* **13** (2006) 600.
- WATERS, S.L., COURSEY, B.M., The Strontium-82 Rb-82 Generator: Preface, *Appl. Radiat. Isot.* **38** (1987) R5.
- WELCH, M.J., MCCARTHY, T.J., The potential role of generator-produced radiopharmaceuticals in clinical PET, *J. Nucl. Med.* **41** (2000) 315–317.
- YANO, Y., ANGER, H.O., Visualization of heart and kidneys in animals with ultrashort-lived ⁸²Rb and positron scintillation camera, *J. Nucl. Med.* **9** (1968) 412.
- YANO, Y., et al., Rb-82 generators for imaging studies, *J. Nucl. Med.* **18** (1977) 46–50.
- YANO, Y., Essentials of a Rb-82 generator for Nuclear-Medicine, *Appl. Radiat. Isot.* **38** (1987) 205–211.

Properties

GRANT, P.M., et al., Half-lives of Sr-82 and Rb-82, *Phys. Rev. C* **18** (1978) 2799–2800.

JUDGE, S.M., et al., A partial decay scheme study of Rb-82 and consequences for radiation-dose measurements, *Appl. Radiat. Isot.* **38** (1987) 185–190.

WOODS, M.J., JUDGE, S.M., LUCAS, S.E.M., The half-life of Rb-82, *Appl. Radiat. Isot.* **38** (1987) 191–192.

Production

MAUSNER, L.F., PRACH, T., SRIVASTAVA, S.C., Production of Sr-82 by proton irradiation of RbCl, *App. Radiat. Isot.* **38** (1987) 181–184.

TARKANYI, F., QAIM, S.M., STOECKLIN, G., Excitation-functions of He-3-particle and alpha-particle induced nuclear-reactions on natural krypton — Production of Sr-82 at a compact cyclotron, *Appl. Radiat. Isot.* **39** 2 (1988) 135–143.

TARKANYI, F., QAIM, S.M., STOECKLIN, G., Excitation-functions of He-3-particle and alpha-particle induced nuclear-reactions on enriched Kr-82 and Kr-83, *Radiochim. Acta* **43** 4 (1988) 185.

QAIM, S.M., Cyclotron production of generator radionuclides, *Radiochim. Acta* **41** (1987) 111–117.

QAIM, S.M., et al., Yield and purity of ^{82}Sr produced via the $^{nat}\text{Rb}(p,xn)^{82}\text{Sr}$ process, *Appl. Radiat. Isot.* **65** (2007) 247–252.

VERESHCHAGIN, Y.I., ZAGRYADSKIY, V.A., PRUSAKOV, V.N., Cyclotron Sr-82 production for medical applications, *Nucl. Instrum. Methods Phys. Res. A* **334** (1993) 246–248.

ZHUIKOV, B.L., GLUSHCHENKO, V.N., KOKHANYUK, V.M., Preparation of ^{82}Sr from a metallic Rb target in a 100 MeV proton beam, *Radiochemistry* **36** 6 (1995) 548.

Chemical processing

AARDANEH, K., VAN DER WALT, T.N., DAVIDS, C., Radiochemical separation of Sr-82 and the preparation of a sterile Sr-82/Rb-82 generator column, *J. Radioanal. Nucl. Chem.* **270** (2006) 385–390.

BILEWICZ, A., et al., Separation of Sr-82 from rubidium target for preparation of Sr-82/Rb-82 generator, *J. Radioanal. Nucl. Chem.* **268** (2006) 485–487.

CKETTE, M.R., RUTH, T.J., VINCENT, J.S., Sr-82 production from metallic Rb targets and development of an Rb-82 generator system, *Appl. Radiat. Isot.* **44** (1993) 917–922.

FASSBENDER, M., et al., Some nuclear chemical aspects of medical generator nuclide production at the Los Alamos hot cell facility, *Radiochim. Acta* **92** (2004) 237–243.

GRANT, P.M., KAHN, M., O'BRIEN, H.A., Isolation of Sr-82 from 200 MeV to 600 MeV proton-irradiated Mo targets for biomedical applications, *J. Inorg. Nucl. Chem.* **37** 2 (1975) 413–417.

KULPRATHIPANJA, S., HNATOWICH, D.J., BROWNELL, G.L., Novel method for removing aluminium from spallation-produced Sr-82, *J. Radioanal. Chem.* **43** 2 (1978) 439–441.

SYLVESTER, P., MOLLER, T., ADAMS, T.W., Improved separation methods for the recovery of Sr-82 from irradiated targets, *Appl. Radiat. Isot.* **64** (2006) 422–430.

THOMAS, K.E., BARNES, J.W., Large-scale isolation of Sr-82 for generator production, *ACS Symp. Ser.* **241** (1984) 123–134.

ZAITSEVA, N.G., DMITRIEV, S.N., Radiochemical separation methods for preparation of biomedical cyclotron radionuclides, *Czech. J. Phys.* **49** Part 2 Suppl. 1 (1999) 825–829.

Generator

BRIHAYE, C., et al., Preparation and evaluation of a hydrous tin(iv) oxide $^{82}\text{Sr}/^{82}\text{Rb}$ medical generator system for continuous elution, *Appl. Radiat. Isot.* **38** (1987) 213–217.

DHAWAN, V., Model for Sr-82/Rb-82 generator elution profiles: A secondary approach to radioassay dosimetry, *Appl. Radiat. Isot.* **38** (1987) 233–239.

EAKINS, M.N., et al., Comparison of cardiogen-82Rb generators manufactured from Sr-82 produced by the Rb-82(p,4n) reaction or the spallation of molybdenum, *Abstr. Pap. Am. Chem. Soc.* **204** 48-NUCL Part 2 (1992).

EPSTEIN, N.J., et al., A Rb-82 infusion system for quantitative perfusion imaging with 3D PET, *Appl. Radiat. Isot.* **60** (2004) 921–927.

GENNARO, G.P., et al., A radionuclide generator and infusion system for pharmaceutical quality Rb-82, *ACS Symp. Ser.* **241** (1984) 135–150.

GENNARO, G.P., et al., Radioanalysis of Rb-82 generator eluates, *Appl. Radiat. Isot.* **38** (1987) 219–225.

GRANT, P.M., WHIPPLE, R.E., O'BRIEN, H.A., KULPRATHIPANJA, S., Influence of carrier strontium level and eluent volume on performance of (Sr-82)-(Rb-82) biomedical generators, *J. Nucl. Med.* **19** (1978) 1250–1255.

HANEY, P.S., GENNARO, G.P., Hydroxyapatite-based Sr-82/Rb-82 generator, *J. Labelled Compd. Radiopharm.* **23** (1986) 1381–1382.

HOOP, B., et al., Myocardial positron scintigraphy with short-lived Rb-82, *IEEE Trans. Nucl. Sci.* **23** 1 (1976) 584–589.

HORLOCK, P.L., et al., The preparation of a rubidium-82 radionuclide generator, *J. Radioanal. Chem.* **64** 1–2 (1981) 257–265.

KLEIN, R., et al., Precision-controlled elution of a Sr-82/Rb-82 generator for cardiac perfusion imaging with positron emission tomography, *Phys. Med. Biol.* **52** (2007) 659–673.

KULPRATHIPANJA, S., HNATOWICH, D.J., BEH, R., Use of inorganic exchangers to improve the Sr-82-Rb-82 generator, *Int. J. Appl. Radiat. Isot.* **30** (1979) 447–449.

MIRZADEH, S., KNAPP, F.F., Biomedical radioisotope generator systems, *J. Radioanal. Nucl. Chem. Articles* **203** 2 (1996) 471–488.

NEIRINCKX, R.D., LOBERG, M.D., New Sr-82-Rb-82 generators based on inorganic adsorbents, *J. Nucl. Med.* **22** (1981) P76–P76.

NEIRINCKX, R.D., KRONAUGE, J.F., GENNARO, G.P., LOBERG, M.D., Evaluation of inorganic adsorbents for the rubidium-82 generator. 1. Hydrous SnO₂, *J. Nucl. Med.* **23** 3 (1982) 245–249.

NEIRINCKX, R.D., KRONAUGE, J.F., LOBERG, M.D., Evaluation of inorganic materials as adsorbents for the Sr-82/Rb-82 generator, *Int. J. Appl. Radiat. Isot.* **34** (1983) 721–725.

SYLVESTER, P., et al., New ion exchange materials for use in a Sr-82/Rb-82 generator, *Appl. Radiat. Isot.* **61** (2004) 1139–1145.

WATERS, S.L., Using a Ge(Li) detector for the absolute assay of positron emitting radionuclides, in particular Sr-82/Rb-82, *J. Labelled Compd. Radiopharm.* **19** (1982) 1379–1381.

WATERS, S.L., et al., Radioassay problems associated with the clinical use of a Rb-82 radionuclide generator, *Int. J. Nucl. Med. Biol.* **10** (1983) 69–74.

WATERS, S.L., et al., A Sr-82/Rb-82 generator suitable for continuous infusion, *J. Labelled Compd. Radiopharm.* **23** (1986) 1378–1380.

YANO, Y., ANGER, H.O., Visualization of heart and kidneys in animals with ultrashort-lived ⁸²Rb and positron scintillation camera, *J. Nucl. Med.* **9** 7 (1968) 412.

YANO, Y., ROTH, E.P., Alumina column Rb-82 generator, *Int. J. Appl. Radiat. Isot.* **30** (1979) 382–385.

YANO, Y., et al., Evaluation and application of alumina column Rb-82 generators, *J. Nucl. Med.* **20** (1979) 684–684.

YANO, Y., BUDINGER, T.F., CHIANG, G., O'BRIEN, H.A., GRANT, P.M., Evaluation and application of alumina-based Rb-82 generators charged with high-levels of Sr-82-85, *J. Nucl. Med.* **20** (1979) 961–966.

YANO, Y., CAHOON, J.L., BUDINGER, T.F., A precision flow-controlled Rb-82 generator for bolus or constant-infusion studies of the heart and brain, *J. Nucl. Med.* **22** (1981) 1006–1010.

YANO, Y., et al., An automated microprocessor-controlled Rb-82 generator for positron emission tomography studies, *ACS Symp. Ser.* **241** (1984) 97–122.

Applications

BATEMAN, T.M., Cardiac positron emission tomography and the role of adenosine pharmacologic stress, *Am. J. Cardiol.* **94** 19D–24D; discussion 24D–25D; review (2004).

BATEMAN, T.M., et al., Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: Comparison with ECG-gated Tc-99m sestamibi SPECT, *J. Nucl. Cardiol.* **13** (2006) 24–33.

LODGE, M.A., et al., Developments in nuclear cardiology: transition from single photon emission computed tomography to positron emission computed tomography, *J. Invasive Cardiol.* **17** (2005) 491–496.

ROSMAN, J., HANON, S., SHAPIRO, M., SCHWEITZER, P., VAN TOSH, A., Relation of T-wave inversion in Q-wave acute myocardial infarction to myocardial viability on resting rubidium-82 and 18-fluoro-deoxyglucose positron emission tomography imaging, *Am. J. Cardiol.* **96** (2005) 42–44.

SCHLEIPMAN, A.R., CASTRONOVO, F.P., Jr., DI CARLI, M.F., DORBALA, S., Occupational radiation dose associated with Rb-82 myocardial perfusion positron emission tomography imaging, *J. Nucl. Cardiol.* **13** (2006) 378–84. Erratum in: *J. Nucl. Cardiol.* **13** (2006) 600.

Chapter 4

RECOVERY, PURIFICATION AND QUALITY EVALUATION OF ^{90}Sr

S.K. SAMANTA

Back End Technology Development Division,
Nuclear Recycle Group,
Bhabha Atomic Research Centre,
Mumbai, India

4.1. INTRODUCTION

Among the various radioisotopes, ^{90}Y has emerged as a promising candidate for use in therapeutic radiopharmaceuticals because of several favourable characteristics, namely, a suitable physical half-life ($T_{1/2}$: 64.1 h), high energy beta rays ($E_{\beta\text{max}}$: 2.28 MeV), no accompanying gamma rays, a stable daughter radionuclide (^{90}Zr) and a simple chemistry. The many possible applications of ^{90}Y include: (a) targeted tumour therapy using radiolabelled monoclonal antibodies [4.1], (b) prevention of restenosis of arteries following angioplasty [4.2, 4.3], and (c) treatment of rheumatoid arthritis (radiation synovectomy) and malignant tumours in the liver using radiolabelled insoluble particles [4.4, 4.5]. This useful radioisotope can be conveniently obtained in a carrier-free form from its longer lived parent ^{90}Sr ($T_{1/2}$: 28.78 a, $E_{\beta\text{max}}$: 0.546 MeV), which is one of the fission products generated during irradiation of U in nuclear reactors. There is considerable interest in the in-house production of ^{90}Y using suitable generators having ^{90}Sr as the parent radionuclide. To meet the ever increasing demand for ^{90}Y in medical research and applications, it is necessary that an adequate supply of ^{90}Sr be available. The demand for ^{90}Sr , however, is not a recent one. In fact, its beneficial utilization in other areas predates its use in medical applications. As early as the 1960s, ^{90}Sr was recovered in large quantities from high level waste in the USA, the United Kingdom and the former Union of Soviet Socialist Republics for use in radioisotope thermoelectric generators (RTGs) and as heat sources. Interest in the large scale separation of ^{90}Sr from radioactive streams has continued since the early years purely from a waste management perspective as well. It is quite possible that the primary source of the present world supply of ^{90}Sr for production of $^{90}\text{Sr}/^{90}\text{Y}$ generators could be traced back to the large inventory already separated to support these other programmes. The available primary ^{90}Sr product, however, needs further processing before it can be considered suitable for use in ^{90}Y generators.

A review of the state of the art of the process of and technology for recovery of ^{90}Sr (and ^{137}Cs) from acidic wastes was published in 1987 [4.6]. IAEA Technical Reports Series No. 356 covered the status up to 1992 [4.7]. A more recent report included a review of technologies for the separation of Sr from alkaline and acidic media from the waste treatment perspective [4.8]. In the present publication, an effort is made to summarize the current status based on published information, with an emphasis on process chemistry aspects of separation, recovery and purification schemes for ^{90}Sr as well as methods for evaluation of product quality.

4.2. BACKGROUND

4.2.1. Generation and radiological properties of ^{90}Sr

Strontium-90 is one of the most important and abundant by-products of ^{235}U fission. With a thermal fission yield of 5.9%, the worldwide operation of nuclear reactors results in the routine production of this important radioisotope at a rate of about 2 MCi/GW(e)-year. Considering that the global installed capacity for nuclear electricity generation is 370 GW(e) and assuming an average capacity factor of 80%, the annual production of ^{90}Sr is about 600 MCi. This huge quantity is present in the spent nuclear fuel discharged from reactors.

Given sufficient time, the $^{90}\text{Sr}/^{90}\text{Y}$ pair comes to secular equilibrium. The growth of ^{90}Y in freshly separated ^{90}Sr is depicted in Fig. 4.1. Over 500 mCi of ^{90}Y can be milked every three days from a 1000 mCi feed solution of ^{90}Sr . Since ^{90}Sr has a long half-life of 28 a, it can be used for several decades to produce ^{90}Y . Only a very small fraction of the projected ^{90}Sr inventory available would be required to meet the current and projected global demand for generators for medical applications.

4.2.2. Radioactive waste as a valuable source for the recovery of ^{90}Sr

The importance of radioactive waste as a valuable resource for the recovery of useful radionuclides has been recognized since the early days of the nuclear industry. A variety of radioactive liquid waste streams are generated during the operation of reactors, reprocessing plants and radioisotope production facilities. The radioactive constituents of the waste streams include fission products, activation products and transuranics. However, not all waste is suitable for the recovery of radionuclides. Depending on the source and nature of the waste, the activities of the radionuclides may vary over a very wide range. If the activity of

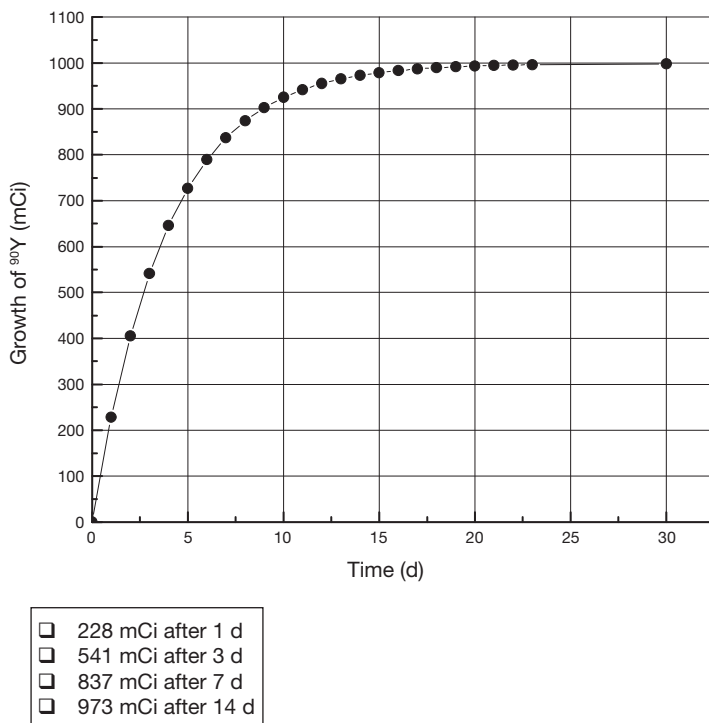
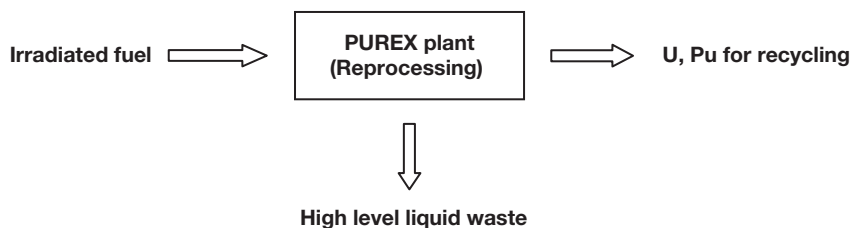


FIG. 4.1. Growth of ⁹⁰Y in 1000 mCi of ⁹⁰Sr.

the desired radionuclide is very low in a particular waste stream, that waste stream is not considered to be a viable source for recovery. From activity considerations, two waste streams that are routinely generated in several facilities around the world qualify as viable sources for recovery of ⁹⁰Sr: the high level liquid waste (HLLW) generated during reprocessing of spent nuclear fuel and the waste from production of ⁹⁹Mo by neutron induced fission of ²³⁵U. The nature and characteristics of these two streams are briefly discussed below.

4.2.3. HLLW from the reprocessing of spent nuclear fuel

As noted above, a large quantity of ⁹⁰Sr is present in the spent fuel discharged from nuclear reactors. In countries following the closed nuclear fuel cycle, the spent fuel is reprocessed to recover Pu and unused U for recycling in reactors. The process used universally at present is based on the PUREX (Plutonium and Uranium Recovery by Extraction) flowsheet. In this process, the irradiated fuel is dissolved in nitric acid, and Pu and U are extracted using an organic solvent consisting of 30% tributyl phosphate (TBP) in dodecane. The



HNO ₃	1–3 M
Actinides	U, Pu, Np, Am, Cm
Fission products	¹³⁷ Cs, ⁹⁰ Sr, ¹⁰⁶ Ru, ¹⁴⁴ Ce, ⁹⁵ Zr, ⁹⁹ Tc, etc.
Chemicals	Fe, Cr, Ni, Mn, Al, Na, Ca, NO ₃ ⁻ , SO ₄ ²⁻ , etc.

FIG. 4.2. Source and nature of HLLW.

aqueous acidic solution that is left behind is concentrated and routed to underground stainless steel tanks for storage. This highly radioactive solution, known as HLLW, contains all the fission products and minor actinides, small quantities of unextracted U and Pu, process chemicals added during reprocessing, and corrosion products (Fig. 4.2).

Worldwide, the accepted strategy for management of HLLW is immobilization in a vitreous matrix followed by ultimate disposal in deep geological repositories. Recently, there has been considerable interest in partitioning strategies aimed at separating groups of radioactive constituents from HLLW for more effective management, particularly with respect to long term radiotoxicity. Adoption of schemes for the separation of radioisotopes such as ¹³⁷Cs and ⁹⁰Sr from HLLW as part of these advanced waste management strategies in the future will make these fission products available for beneficial utilization in industry and healthcare applications.

As indicated in Fig. 4.2, HLLW is a highly radioactive acidic solution having a complex composition that includes a number of radioactive and non-radioactive constituents. The exact radiochemical composition of HLLW depends on the reprocessing flowsheet and the properties of the spent fuel, including its type, burnup, irradiation profile and cooling period. Some typical values for ⁹⁰Sr in spent fuel and HLLW in India are shown in Table 4.1. The activity is expected to be higher in HLLW from reprocessing plants in those countries where the spent fuel originates from light water reactors with much higher burnup.

The recovery of ⁹⁰Sr from HLLW leads to the chemical separation of Sr as an element, and thus the product will include the other Sr isotopes generated in the irradiated fuel and also present in the waste. Some relevant data on the three Sr isotopes generated during thermal fission of ²³⁵U are summarized in Table 4.2.

TABLE 4.1. TYPICAL CONCENTRATION OF ^{90}Sr IN SPENT FUEL AND HLLW IN INDIA

Spent fuel source	Burnup (MWd/Te heavy metal)	^{90}Sr in spent fuel (kCi/Te heavy metal)	^{90}Sr in HLLW (Ci/L)
Research reactor	1000	3	2–10
Power reactor (PHWR)	6700	20	5–20

TABLE 4.2. Sr ISOTOPES GENERATED DURING THERMAL FISSION OF ^{235}U

Sr isotope	$T_{1/2}$	Specific activity (Ci/g)	Fission yield (%)
^{88}Sr	Stable	Not applicable	3.65
^{89}Sr	50.5 d	2.9×10^4	4.81
^{90}Sr	28.78 a	138	5.93

Because of its relatively short half-life, the activity of ^{89}Sr is expected to be insignificant in aged HLLW. Strontium-88 formed by fission will be present in the ^{90}Sr isolated from fission products. In addition, small traces of stable Sr introduced as an impurity in U and the process chemicals added during reprocessing will eventually end up in the recovered ^{90}Sr product, contributing the following stable isotopes: ^{84}Sr , ^{86}Sr , ^{87}Sr and ^{88}Sr . Since ^{88}Sr is the predominant stable isotope with a natural abundance of 82.56%, the ^{90}Sr product will contain ^{88}Sr as the major isotopic impurity [4.9]. For example, based on analysis, the Sr present in PUREX waste at Hanford (Richland, Washington, USA), was reported to have the following isotopic composition: ^{90}Sr ($56.1 \pm 1.2\%$), ^{88}Sr ($42.2 \pm 1.2\%$), ^{87}Sr ($0.68 \pm 0.11\%$) and ^{86}Sr ($0.93 \pm 0.13\%$) [4.10]. Because of this isotopic dilution and the presence of small quantities of other chemical impurities, the specific activity of ^{90}Sr recovered from HLLW is found to be substantially lower than 138 Ci/g, and generally in the range of 30–50 Ci/g [4.11–4.13].

4.2.4. Waste from the production of ^{99}Mo

As has already been noted, the quantity of ^{90}Sr required to meet the demand for preparation of ^{90}Y generators is very small compared with the quantity that is present in HLLW generated from the reprocessing of spent nuclear fuel. Countries with reprocessing programmes thus have a ready abundant source for the recovery of ^{90}Sr for medical applications. On the other hand, many countries

have industrial scale programmes for the production of ^{99}Mo by neutron induced fission of ^{235}U in high enriched uranium (HEU) and low enriched uranium (LEU) targets. In the absence of a reprocessing programme, the radioactive waste generated during production of ^{99}Mo can also be exploited as a relatively modest source for the recovery of ^{90}Sr in quantities that would be adequate to meet local requirements. An IAEA publication on the management of radioactive waste from ^{99}Mo production advocates due consideration of the possible recovery of other valuable radionuclides from such waste [4.14]. An examination of the data included in that publication shows that multicurie quantities of ^{90}Sr are available annually for recovery from such waste, after sufficient ageing to allow for the decay of the ^{89}Sr also present in the waste. In the Belgoprocess facility for ^{99}Mo production, for example, about 38 Ci of ^{90}Sr was present in the waste at an average concentration of about 15 mCi/L, according to the waste generation record [4.14]. Unfortunately, no serious effort seems to have been made anywhere to exploit HLLW as a source for recovery of ^{90}Sr , except for one reported study carried out in Argentina, which is discussed later in this publication (Section 4.4.4).

4.3. NUCLEAR DECAY CHARACTERISTICS

As noted above, the utility of ^{90}Y in medical applications is due to the favourable decay characteristics of the $^{90}\text{Sr}/^{90}\text{Y}$ parent–daughter pair. The decay scheme is shown in Fig. 4.3. Yttrium-90 has favourable nuclear decay characteristics ($T_{1/2}$: 64.1 h, $E_{\beta\text{max}}$: 2.28 MeV), no accompanying gamma rays, and a stable decay product (^{90}Zr). The parent radionuclide ^{90}Sr ($T_{1/2}$: 28.78 a) decays via beta emission of $E_{\beta\text{max}}$ 0.546 MeV.

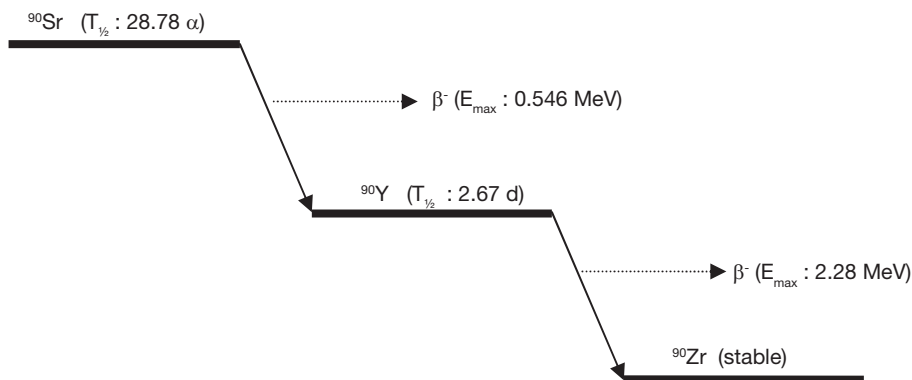


FIG. 4.3. Decay scheme for $^{90}\text{Sr}/^{90}\text{Y}$.

4.4. PROCESSES FOR THE RECOVERY OF ^{90}Sr FROM RADIOACTIVE WASTE

The recovery of ^{90}Sr from HLLW entails its separation from other radioactive and inert constituents present in the waste. Efforts continue aimed at developing suitable schemes for the effective separation of ^{90}Sr from a variety of complex waste streams. Some of the processes have been used for industrial scale recovery of substantial (megacurie) quantities of ^{90}Sr . For example, in the past, at the Hanford site in the USA, defence waste was processed to recover nearly 40 MCi of ^{90}Sr , which is currently stored as SrF_2 encapsulated in double-walled canisters under water [4.6]. Most of these initial efforts were made with the primary objective of meeting the requirements projected at the time, without paying adequate attention to the consequences of the separation process for further management of the residual waste. However, it is desirable that a viable scheme for the routine recovery of any radioisotope from HLLW should also satisfy the following conditions:

- (a) Isolation of the desired radioisotope with high radioactive concentration, radionuclidic purity and chemical purity;
- (b) Simple process steps using readily available chemical reagents;
- (c) Safe and effective management of all secondary waste streams;
- (d) The radioisotope depleted HLLW is not more difficult to manage than it was before separation of the desired radioisotope.

A survey of the literature reveals that separation processes for the recovery of ^{90}Sr fall into four major categories: precipitation, ion exchange, solvent extraction and extraction chromatography. These processes have been used not only for the initial separation of ^{90}Sr from HLLW but also for its purification before use in ^{90}Y generators. The various types of generator also utilize these same techniques for the separation of ^{90}Y from ^{90}Sr and for purification of the ^{90}Y product before use in medical applications. Figure 4.4 shows the general scheme for separation and purification, along with the techniques commonly used at different stages. The processes used for the primary separation of ^{90}Sr from radioactive liquid waste are discussed below.

4.4.1. Precipitation

Precipitation has long been among the tools most widely used by radiochemists in their work on the separation and analysis of radioactive elements. The possibility of incorporating a variety of chemical manipulations to achieve the required separations is a major advantage of this technique.

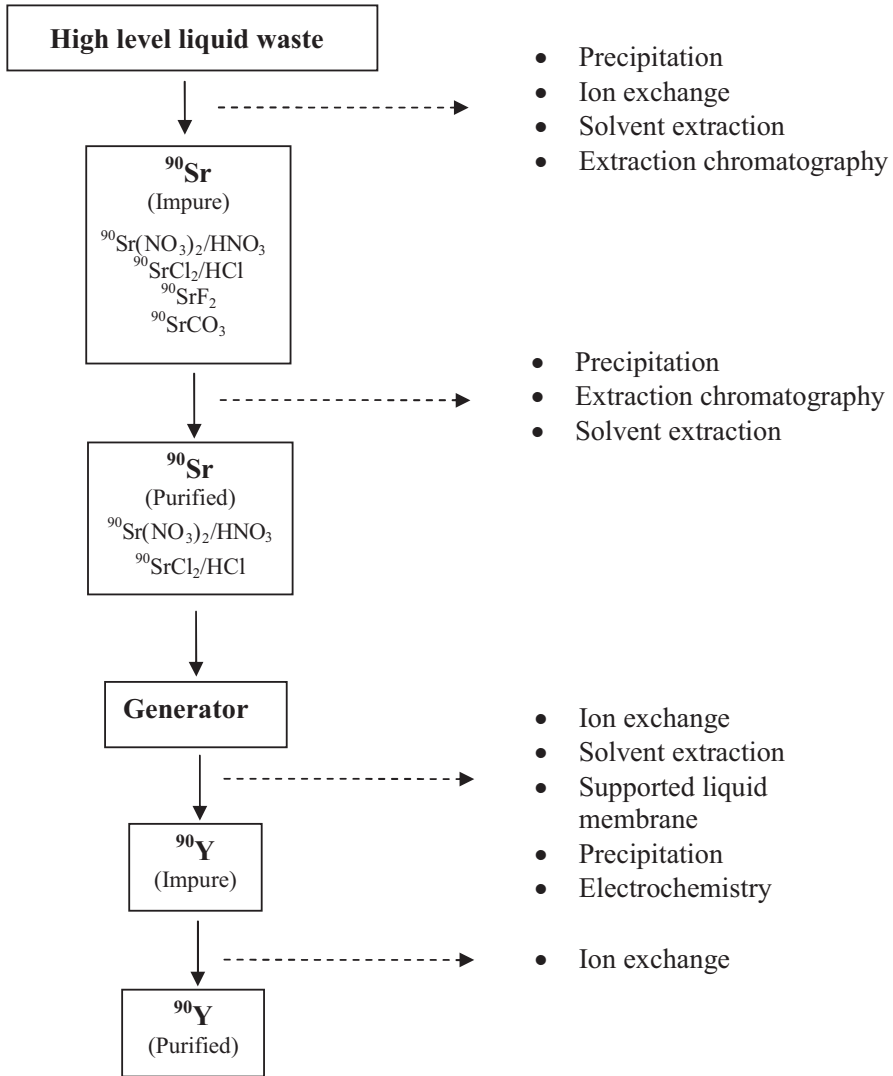


FIG. 4.4. General scheme for the separation and purification of ⁹⁰Sr and ⁹⁰Y.

Precipitation processes have also been used for production scale separations. For operations involving highly radioactive solutions, handling of the precipitate and efficient solid–liquid separation are the areas requiring careful attention. A brief description of some of the precipitation processes used at various places over the years is given below.

4.4.1.1. Lead sulphate carrier precipitation (Hanford, USA)

PbSO₄ acts as an effective carrier for traces of fission product Sr [4.9]. A process based on this principle was developed and used at the Hanford site in the USA to separate ⁹⁰Sr from PUREX acid waste and acidified sludge waste [4.6, 4.15, 4.16]. In this process, Na₂SO₄, NaOH and Pb(NO₃)₂ are added to the acidic waste in sufficient quantities to give the following composition of the resulting solution:

SO₄²⁻: 0.67–3M
Pb²⁺: 0.02M
pH: 0.4–4

Glycolic acid (CH₂OH.COOH) is also added at a concentration of about 0.5M to prevent the precipitation of Fe³⁺ ions (present in the waste) by complexation. Digestion of the solution at 80°C along with added chemical reagents lead to the formation of a precipitate and to removal of Sr and rare earth (RE) fission product activities from the solution. While Sr is carried down by lead sulphate (PbSO₄), the rare earths are removed as double salts with sodium sulphate, Na₂SO₄.RE₂(SO₄)₃.2H₂O. The precipitate is separated by centrifugation. The resulting cake is washed with 1M Na₂SO₄ solution and then digested with NaOH-Na₂CO₃ solution at 80°C to remove Pb and to convert the sulphate cake to carbonate form by metathesis. The cake is then washed with dilute Na₂CO₃ solution. Addition of nitric acid to the washed cake leads to decomposition of the carbonates and to dissolution of Sr and rare earths as nitrates. Over 95% recovery of the Sr present in the feed solution is achieved in this initial separation. The solution obtained at this stage has a Sr concentration that is 9–10 times higher than that of the feed solution and is also largely free of other undesirable inactive and radioactive constituents (e.g. Fe, Na, Al, Mg, Mn, Cr, Ni, Ca, Zr-Nb, Ru, Cs).

The rare earths are removed from this solution as their oxalates by addition of oxalic acid. The concentration of oxalic acid is maintained at 0.35M. After separation of the oxalate precipitate, the solution is concentrated and stored as the Sr product solution. Figure 4.5 shows a simplified process flow diagram.

The PbSO₄ carrier precipitation technique outlined above was scaled up and used at the Hanford site in the 1960s to separate megacuries of ⁹⁰Sr from PUREX acid waste and acid dissolved sludge. Utilization in radioisotope applications required further purification of this concentrate. A solvent extraction process developed and used for purification is discussed later in this report (Section 4.4.3.1).

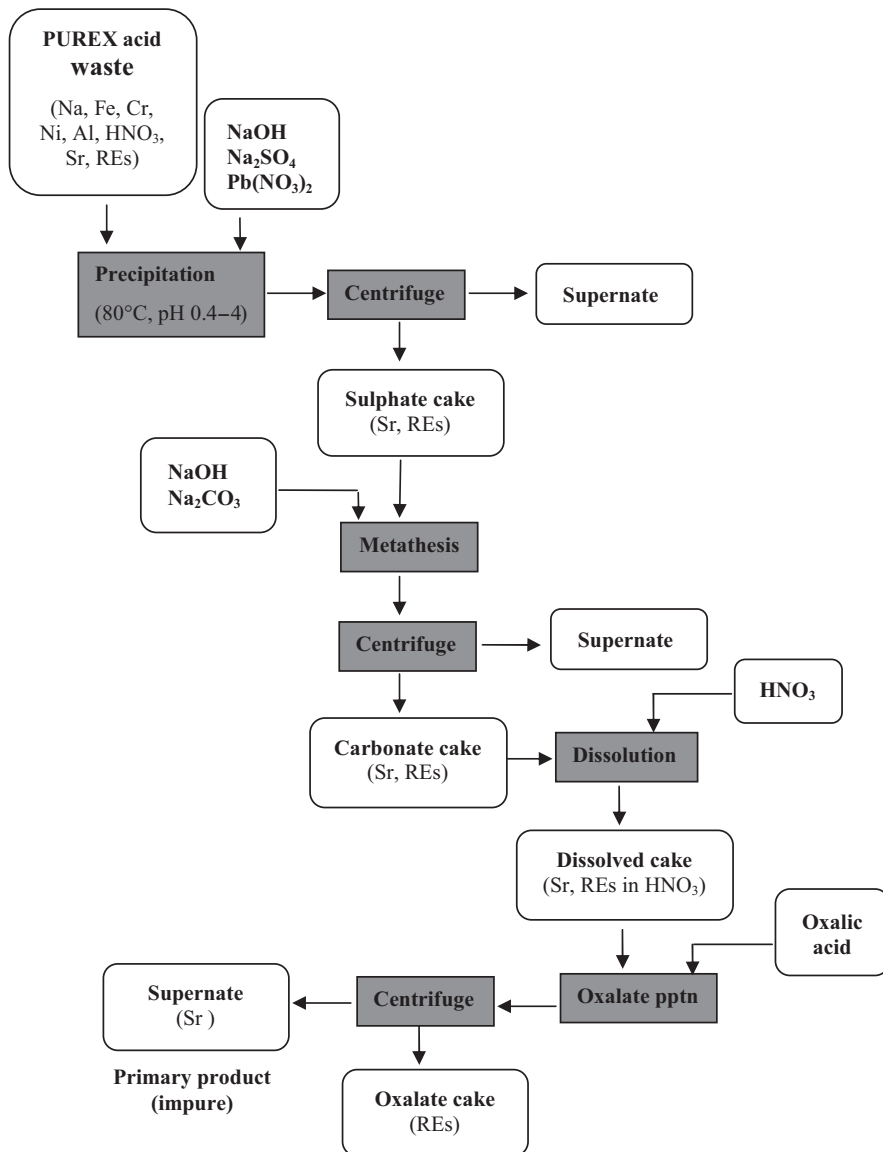
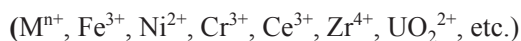
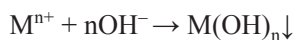


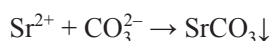
FIG. 4.5. Lead sulphate carrier precipitation process for separation of radiostrontium from HLLW.

4.4.1.2. Hydroxide-carbonate precipitation (PNNL, USA)

In this process, Sr is isolated from HLLW by precipitation as strontium carbonate [4.12]. Before this precipitation can be carried out, acidic HLLW has to be made alkaline by addition of sodium hydroxide. This pretreatment leads to the precipitation of hydroxides of almost all active and inactive metal ions except alkali and alkaline earth metal ions:



The supernatant solution contains ^{90}Sr and ^{137}Cs as the major radioisotopes. Addition of Na_2CO_3 to this solution results in the precipitation of SrCO_3 :



The SrCO_3 precipitate is the primary product, which must then be subjected to further processing for purification before it can be used for preparation of ^{90}Y generators for medical applications. A simplified process scheme is shown in Fig. 4.6. The purification process is discussed later in this report (Section 4.5.2).

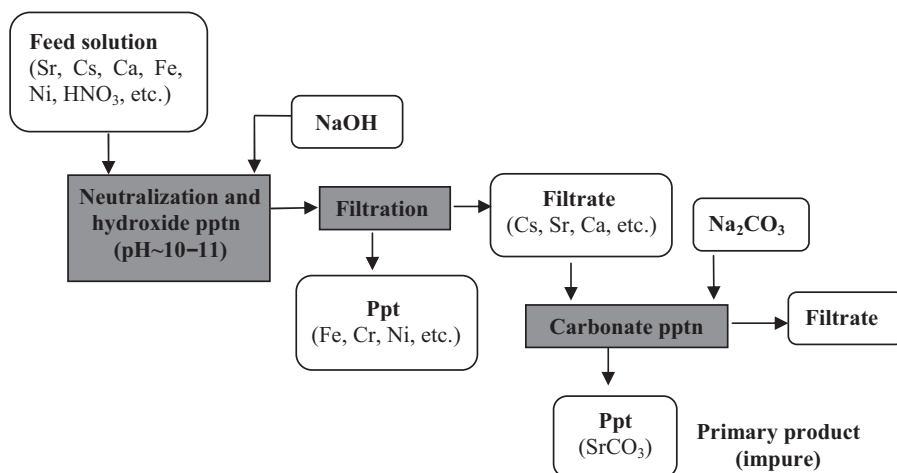


FIG. 4.6. Hydroxide-carbonate precipitation process for separation of radiostrontium from HLLW.

4.4.1.3. Hydroxide-carbonate precipitation (BARC, India)

A multistep procedure that evolved over a period of few years has been in use at the Bhabha Atomic Research Centre (BARC), India, for the recovery and supply of ^{90}Sr for use in ^{90}Y generators for medical applications [4.17]. In this process, acidic HLLW generated at a PUREX plant for reprocessing research reactor fuel and containing about 2–3 Ci/L ^{90}Sr is processed in small batches for the separation and purification of ^{90}Sr . In view of the complex nature of the HLLW, a multistep process involving solvent extraction and ion exchange is necessary to separate the fission product in a reasonably pure form, free from major chemical and radiochemical impurities. The initial separation is followed by radiochemical procedures involving precipitation reactions for further purification and concentration of the ^{90}Sr product.

In a typical procedure, the first step is the removal of U, Np and Pu by contacting the waste with 30% TBP in n-dodecane. This is followed by one more step of solvent extraction with 0.2M CMPO/1.2M TBP in n-dodecane to remove Am and the trivalent fission product lanthanides. The actinide and lanthanide depleted HLLW is then passed through a column containing a synthetic mordenite or granulated ammonium molybdophosphate to selectively remove ^{137}Cs , another high yield fission product present in the waste. The resulting solution contains ^{90}Sr as the major activity along with small quantities of ^{106}Ru , ^{125}Sb and ^{137}Cs .

Removal of these radionuclides is carried out using repeated scavenging with $\text{Fe}(\text{OH})_3$ and precipitation of ^{90}Sr as SrCO_3 with the help of added Sr(II) carrier. The purified product is obtained in a concentrated form after final dissolution of the precipitate in a small volume of dilute HNO_3 . The steps involved in the process are shown in Fig. 4.7.

Up to 250 mL of HLLW has been processed in batches to recover ^{90}Sr in a concentrated form and having high radionuclidic purity. The product is used in a novel membrane based generator [4.18, 4.19] as well as in an electrochemical generator [4.20] to routinely produce ^{90}Y for radiopharmaceutical research.

4.4.1.4. Strontium nitrate precipitation (Radiochemical Centre, UK)

The very low solubility of $\text{Sr}(\text{NO}_3)_2$ in concentrated HNO_3 is widely utilized for separation and analysis of ^{90}Sr in environmental and effluent samples [4.9]. The same property can also be utilized for separation of ^{90}Sr from fission product solutions. When the concentration of HNO_3 in a fission product solution is increased to 60–70% by evaporation or by addition of fuming HNO_3 , the ^{90}Sr present in the solution precipitates as $\text{Sr}(\text{NO}_3)_2$. Inactive Ba present in the solution also precipitates as $\text{Ba}(\text{NO}_3)_2$ under these conditions. The separation and recovery

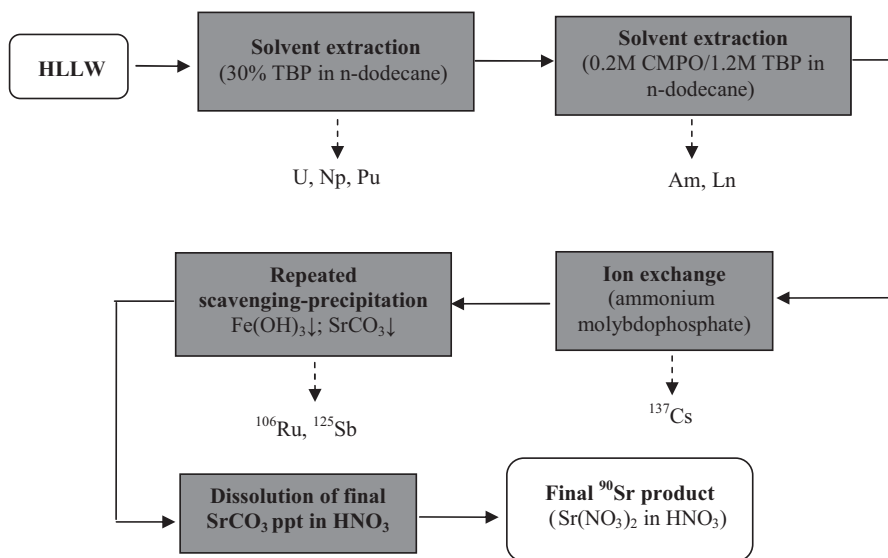


FIG. 4.7. Hydroxide-carbonate precipitation process for separation of radiostrontium from HLLW.

of ^{90}Sr can be made more complete by the addition of $\text{Pb}(\text{NO}_3)_2$ as a carrier. This principle was the basis of a method used at the Radiochemical Centre in Amersham, UK, for the production of ^{90}Sr on the scale of 10 Ci per batch [4.21]. In the procedure followed at Amersham, a nitric acid solution of aged fission products was concentrated after addition of $\text{Pb}(\text{NO}_3)_2$. The concentrated solution was cooled, and the precipitate of $\text{Sr}(\text{NO}_3)_2$ and $\text{Pb}(\text{NO}_3)_2$ was separated and dissolved in dilute HNO_3 . The nitrates were then reprecipitated by adding fuming nitric acid to this solution. The precipitate was washed with 80% HNO_3 and dissolved in dilute HNO_3 . The precipitation and washing steps were repeated. Finally, the mixed precipitate was dissolved in 2.5M HNO_3 and the Pb was removed by electrodeposition on a Pt gauze anode. The product was $>99.9\%$ $^{90}\text{Sr} + ^{90}\text{Y} + ^{89}\text{Sr}$. The main radioactive impurity was ^{144}Ce . The alpha activity was <9 nCi/Ci ^{90}Sr .

4.4.2. Ion exchange

One of the most widely used methods for the removal of cations from aqueous media is based on the use of fixed bed columns filled with cation exchange resins. Conventional cation exchange resins are based on a poly(styrene-divinylbenzene) matrix with sulphonic acid functional groups. Such resins are routinely used along with anion exchange resins for the demineralization of water. Since such resins do not show high selectivity

differences between different cations, their use in the selective recovery of a particular cation is possible by suppressing the exchange of other cations using complexants and/or by selective stripping of the desired cation from the loaded column. The example discussed below illustrates the use of a conventional cation exchange resin for large scale separation of ^{90}Sr .

4.4.2.1. *Dowex 50W-X12 (Hanford, USA)*

A cation exchange process was used in 1961 at the Hanford site in the USA to produce nearly 1 MCi of ^{90}Sr for use as thermoelectric power sources [4.22, 4.23]. Dowex 50W-X12, a poly(styrene-divinylbenzene) sulphonic acid resin, was used. The feed to the ion exchange column was the impure ^{90}Sr product solution obtained after lead sulphate carrier precipitation of ^{90}Sr from acidic PUREX waste, as discussed above. Besides being contaminated with $^{95}\text{Zr-Nb}$ and $^{144}\text{Ce-Pr}$, the feed had Ca, Ba, Fe, Pb and Na as chemical impurities. The activity of ^{90}Sr in the feed was 26 Ci/L. The initial step involved addition of N-hydroxyethylethylenediamine triacetic acid (HEDTA) to the feed and adjustment of the pH to 4 with NH_4OH . The HEDTA helped to complex Ca, Fe and Pb and part of the Zr-Nb and prevent their adsorption on the column. After a water wash, the Sr was eluted from the column using 0.015M EDTA at pH8.5. The product had very low contamination with $^{95}\text{Zr-Nb}$ ($<5 \times 10^{-5}$ Ci/Ci ^{90}Sr) and $^{144}\text{Ce-Pr}$ ($<1 \times 10^{-5}$ Ci/Ci ^{90}Sr). The chemical purity of the product was 95% Sr, of which 56% was present as the ^{90}Sr isotope. Though adequate for thermoelectric power sources, additional purification would be required before such a product could be used in $^{90}\text{Sr}/^{90}\text{Y}$ generator applications.

4.4.3. Solvent extraction

A number of solvent extraction processes have been developed over the years for the separation of ^{90}Sr from complex radioactive waste streams.

4.4.3.1. *HDEHP (ORNL and Hanford, USA)*

A solvent extraction process based on bis(2-ethylhexyl)phosphoric acid (HDEHP) in a hydrocarbon diluent with TBP as a modifier was developed at Oak Ridge National Laboratory (ORNL), Oak Ridge, Tennessee, USA, for the recovery and purification of ^{90}Sr from radioactive waste streams [4.8]. The extractant (Fig. 4.8) is not very specific and works only under weakly acidic (pH4–5) conditions.

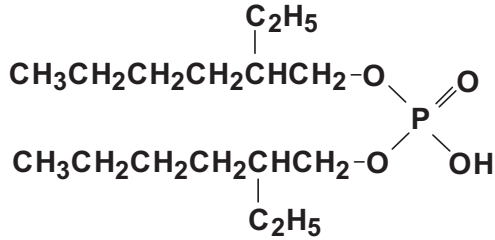
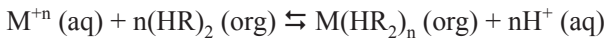


FIG. 4.8. Structure of bis(2-ethylhexyl)phosphoric acid (HDEHP).

HDEHP exists as a hydrogen bonded dimer in non-polar diluents and acts like a liquid cation exchanger in which a H ion is displaced by the extracted metal ion [4.16]. The general reaction can be written as follows:



where R represents the bis(2-ethylhexyl) phosphate anion, $(\text{HR})_2$ represents the dimerized HDEHP and (aq) and (org) refer to the aqueous and organic phases, respectively.

The reaction given above shows that low acidity favours the uptake of metal ions. Proper control of pH is essential in using HDEHP for extraction of a desired metal ion free from other impurities.

The process was developed further for plant scale application and used at Hanford, USA, to recover and purify over 40 MCi of ^{90}Sr from acidified PUREX process sludge [4.6]. In this process, various complexing agents (e.g. EDTA, citric acid) were added to the acidic waste to prevent the co-extraction of Fe, Al and other metal ions along with Sr. After addition of the complexing agents, the pH of the feed was adjusted to 4–5 by addition of NaOH. Upon contact with the solvent (0.4M HDEHP + 0.2M TBP + dodecane), Sr, Ca and rare earth fission products were extracted into the organic phase. The loaded Sr was stripped by using dilute nitric acid.

The HDEHP process was the first to be used for the industrial scale recovery of ^{90}Sr . However, the process resulted in the generation of secondary waste streams containing high concentrations of various complexing agents which were difficult to treat. Moreover, the process is not suitable for high level waste having nitric acid in molar concentrations, as is usually the case.

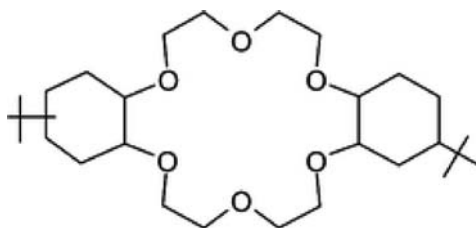


FIG. 4.9. Structure of 4,4'(5')-di-*t*-butylcyclohexano-18-crown-6 (DtBuCH18C6).

4.4.3.2. Macrocyclic polyethers (ANL/INEEL, USA; Mayak, Russian Federation)

Macrocyclic polyethers or crown ethers exhibit high selectivity for metal ions based on the shape and size of their cavities. A very effective process known as SREX (strontium extraction) was developed at Argonne National Laboratory (ANL), Argonne, Illinois, USA, in the early 1990s for the selective separation and recovery of ^{90}Sr from acidic waste streams [4.24]. In this process, Sr is extracted from acidic solutions ($\geq 1\text{M HNO}_3$) using a 0.2M solution of 4,4'(5')-di-*t*-butylcyclohexano-18-crown-6 (DtBuCH18C6) in 1-octanol. The structure of DtBuCH18C6 is shown in Fig. 4.9.

The *cis-syn-cis* isomer of the crown ether is the most effective one for extraction of Sr. After extraction, Sr is readily stripped from the organic phase using either water or very dilute ($< 0.05\text{M}$) HNO_3 . Batch tests carried out using actual waste (acidified Hanford tank sludge) have shown that ^{90}Sr can be separated from the bulk waste components [4.25]. In one set of tests, more than 99% of the Sr could be extracted from feed solution containing 3 mCi/L of ^{90}Sr activity. Barium and Pb were also extracted along with the Sr. The loaded Sr could be easily stripped with 0.01M HNO_3 .

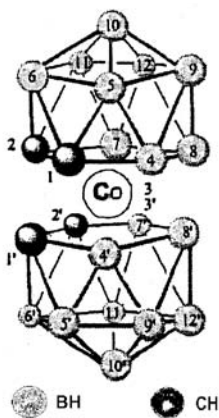
A modified SREX process was subsequently developed [4.26] in which 1-octanol was replaced by Isopar L (a mixture of $\text{C}_{10}\text{-C}_{12}$ isoparaffinic hydrocarbons) and tributyl phosphate (TBP) was added as a phase modifier. Countercurrent flowsheet testing with actual acidic waste at the Idaho National Engineering and Environmental Laboratory (INEEL) using 0.15M 4,4'(5')-di-*t*-butylcyclohexano-18-crown-6 and 1.5M TBP in Isopar L showed that ^{90}Sr could be separated with 99.995% efficiency. Lead and alpha activity were also extracted with high efficiency. Almost all the loaded ^{90}Sr (99.99%) and a small fraction of Pb were stripped using 0.05M HNO_3 . A process based on di-cyclohexano-18-crown-6 was used in pilot industrial tests at the Mayak Production Association, Russian Federation, to recover 0.5 MCi of ^{90}Sr from 90 m^3 of high level waste [4.27]. Loaded Sr was stripped with water, leading to a sixfold concentration.

4.4.3.3. Cobalt bis(1,2-dicarbollides) (Czech Republic; Mayak, Russian Federation)

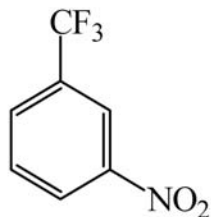
1,2-dicarbollide ($C_2B_9H_{11}^{2-}$) is a polyhedral carborane anion that is known to form sandwich compounds with many metal ions. For example, interaction with Co^{3+} ions results in $[Co(C_2B_9H_{11})_2]^-$, known as cobalt bis(1,2-dicarbollide) [4.28]. $[Co(C_2B_9H_{11})_2]^-$ is a strongly basic hydrophobic anion that can extract metal ions from aqueous solutions into an organic phase by forming ion pairs (e.g. $[Cs^+][Co(C_2B_9H_{11})_2]^-$). The extraction properties of this compound have been extensively investigated in the Czech Republic and the Russian Federation. Initial studies resulted in the development of a solvent extraction process for recovery of Cs^+ ions from acidic waste using cobalt bis(1,2-dicarbollide) in a polar diluent such as nitrobenzene [4.29]. Strontium is not extracted to any significant degree under these conditions because of its hydrophilic character. However, addition of polyethylene glycol (PEG) to the solvent leads to the extraction of Sr^{2+} ions as well [4.30]. PEG exerts a synergistic effect by associating with Sr^{2+} ions to form a hydrophobic species that is extracted into the organic phase containing the dicarbollide anion [4.31]. The extraction of Cs is not affected by the addition of PEG.

Although cobalt bis(1,2-dicarbollide) has high chemical and radiation stability, the chlorinated derivative shows even greater stability. Hence chlorinated cobalt dicarbollide (CCD) has been used in most of the applications. Another recent improvement is the replacement of toxic nitrobenzene with metanitrobenzotrifluoride, a less toxic polar diluent [4.32]. A CCD based industrial solvent extraction process for separation of Cs and Sr has been implemented in UE-35 (Mayak, Russian Federation), which is the first commercial facility in the world for the recovery of radionuclides [4.33, 4.34]. The process uses 0.06–0.15M CCD and 0.03–0.07M polyethylene glycol (PEG-400) in metanitrobenzotrifluoride (F-3) as a diluent. In several campaigns since the commissioning of the facility in 1996, more than 1000 m³ of high level waste has been processed, leading to the separation of nearly 15 MCi of ¹³⁷Cs and ⁹⁰Sr. The structures of the various components of this extraction system are shown in Fig. 4.10.

In the CCD process, the combined stripping of Cs^+ and Sr^{2+} ions is carried out using 5.0–6.0M HNO_3 . The extractant is regenerated using 8M HNO_3 containing 20 g/L hydrazine. The concentrate obtained in the campaigns at Mayak mentioned above was vitrified to produce glass having a higher specific activity than would have been obtained without separation of these two fission products. In recent times, the emphasis has been on combining CCD with other

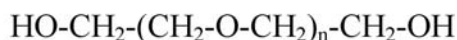


Cobalt bis(1,2-dicarbollide)



F-3

Metanitrobenzotrifluoride



Polyethylene glycol

FIG. 4.10. Components of the CCD based extraction system.

extractants to develop universal extraction (UNEX) flowsheets for simultaneous extraction of Cs, Sr, lanthanides and actinides from high level waste, followed by stripping to obtain either a combined product or individual fractions, as desired [4.35, 4.36]. Although these efforts are primarily focused on more effective waste management, the CCD process can be adapted to the recovery of ^{90}Sr from high level waste, for example, by prior removal of ^{137}Cs using CCD without PEG or by selective stripping after combined extraction of Cs and Sr using CCD-PEG extraction. It should be noted that other waste constituents are also co-extracted; for example, substantial quantities of Ba and Pb and minor quantities of Na, K, Ca, Fe, etc., are also extracted and are recovered in the strip product [4.31]. Hence pure ^{90}Sr can be obtained only after further processing of the strip product obtained in this process.

4.4.4. Extraction chromatography

Extraction chromatography is a convenient column chromatographic technique that utilizes selective ligands sorbed on or covalently bonded to porous solid supports in the form of small granules or beads 50–150 μm in size. A Sr-selective extraction chromatographic resin and its utilization for the recovery of ^{90}Sr are discussed below.

4.4.4.1. Sr-SpecTM resin (Eichrom Industries, USA)

For the separation of Sr, a very effective extraction chromatographic resin has been developed by sorbing a solution of 4,4'(5')-di-*t*-butylcyclohexano-18-crown-6 (DtBuCH18C6) in 1-octanol on an inert polymeric substrate [4.37]. The product is available commercially (Eichrom Industries, USA) as Sr-SpecTM resin (or simply 'Sr Resin'), which is made by impregnating Amberchrom CG-71 (similar to Amberlite XAD-7, a polyacrylate resin) with a 1M solution of DtBuCH18C6 in 1-octanol at a loading of 40% by weight [4.38, 4.39]. The extraction properties of this resin are similar to those of SREX solvent in liquid-liquid extraction. Apart from Sr, the resin shows affinity for Ba(II), Pb(II), Pu(IV), Np(IV) and Po(IV), but selective separation of Sr can be achieved by properly adjusting the loading and elution conditions [4.38]. Although originally conceived as an analytical tool for the separation and concentration of ⁹⁰Sr in biological and environmental samples, the resin has also been studied for its possible use in separation of ⁹⁰Sr from radioactive waste streams.

Sr-SpecTM resin has been tested for removal of ⁹⁰Sr from actual high level waste sludge at Hanford, USA [4.40]. The sludge, resulting from neutralization of the solution obtained after chemical decladding of Zircaloy-clad spent U fuel, contained Zr(OH)₄ and NaF as the major inert constituents. The radioactive constituents include U, fission products (e.g. ¹³⁷Cs, ⁹⁰Sr) and transuranics (Pu, Am). For this test, a portion of the sludge was dissolved in HNO₃/HF solution. The solution was passed through a TRU-SpecTM resin column to remove Am and Pu. The effluent from the TRU-SpecTM column was used as feed to the Sr-SpecTM resin column after adding ⁸⁵Sr (as a gamma emitting radiotracer for Sr) and adjusting the acidity to 3.5M HNO₃. The concentration of Sr in the feed was 7.4×10^{-6} M. The column containing 1.43 mL of Sr-SpecTM resin was conditioned by passing 5 mL of 3M HNO₃ through it. This was followed by the loading of 9.9 mL of waste feed solution at about 8 bed volumes per hour. The loaded bed was washed with 3 mL of 3M HNO₃ and then eluted with 9 mL of distilled water. The results showed that Sr was effectively separated from the bulk waste constituents. No ⁸⁵Sr was detected in the effluent. Some Ba was found to accompany Sr; however, it is possible to eliminate this problem by loading under more acidic conditions.

Recent tests in the Russian Federation using highly active solution obtained after dissolution of spent fuel elements have shown that Sr Resin is very effective in the separation and recovery of ⁹⁰Sr for use as a raw material in ⁹⁰Y generators [4.41]. Spent fuel elements having 3% burnup were cooled one year and then chopped and dissolved in 8M HNO₃. The feed solution (350–400 mL) for ⁹⁰Sr recovery tests was obtained after adjustment of the acidity to 3.5M HNO₃. This solution contained 100–150 g/L U, 5–10 Ci/L ⁹⁰Sr and other fission products. The process steps were as follows:

Primary separation. The feed solution was passed through a column containing 30 mL of conditioned Sr Resin (100–150 μ) at a flow rate of 50–60 mL/h. This was followed by washing with 150 mL of 3.5M HNO₃ at 120–150 mL/h. The loaded Sr was then eluted by passing 200 mL of distilled water through the column at a flow rate of 175–200 mL/h. This simple operation resulted in a Sr product having a radionuclidic purity of about 97%. Another purification step was performed to remove the small quantities of fission product impurities such as ^{134/137}Cs, ¹⁴⁴Ce-¹⁴⁴Pr, ¹⁰⁶Ru-¹⁰⁶Rh, ⁹⁵Zr-⁹⁵Nb and ¹²⁵Sb.

Secondary purification. The eluate from the primary separation was evaporated to dryness and the residue was dissolved in 200 mL of 3.0–3.5M HNO₃. This solution was then passed through another column containing 30 mL of Sr Resin at a flow rate of 100–120 mL/h. Washing and elution were performed as above.

Final purification. This step was essentially meant to remove traces of organics (leached from the resin) from the product. The product solution from the secondary purification step was passed through a column containing 20 mL of Dowex 50W-X8 (100 mesh) cation exchange resin at a flow rate of 180–200 mL/h. After washing with 200 mL of 0.2M HNO₃ (or HCl), the Sr was eluted with 200 mL of 4M HNO₃ (or HCl) at 150–170 mL/h. The product solution was evaporated to dryness and the residue was dissolved in HNO₃ or HCl as per the requirement. No radionuclides were detected in the final product. The content of inert metal ions was <30 ppm. This high purity ⁹⁰Sr is suitable for use in ⁹⁰Y generators.

As noted above, radioactive waste from the production of ⁹⁹Mo is a promising source for the recovery of limited quantities of ⁹⁰Sr for generator applications. A study carried out in Argentina examined the possibility of recovering ⁹⁰Sr as part of a process for ⁹⁹Mo production from LEU fission [4.42]. Assuming 20% enrichment, a thermal neutron flux of 1.1×10^{14} n·cm⁻²·s⁻¹ and an irradiation time of 120 h, it was estimated that about 100 mCi of ⁹⁰Sr would be generated per U target miniplate at the end of each irradiation. Because of the high activity of ⁸⁹Sr generated at the same time and the complexity of chemical operations, it is of no utility to carry out separation of Sr during the course of ⁹⁹Mo production. However, ⁸⁹Sr decays to negligible levels after a few years, and then the waste solution remaining after separation of ⁹⁹Mo can be processed to recover ⁹⁰Sr. The use of LEU in place of HEU in this case implies that Sr has to be separated from much larger quantities of U. Extraction chromatography using Sr Resin (Eichrom) was studied by the authors, using test solutions containing representative high concentrations of U and radiotracers of other elements. It was found to be possible to recover Sr in a small volume of dilute nitric acid. Finally, in a pilot experiment using solution obtained from dissolved irradiated LEU after irradiation, it was demonstrated that ⁹⁰Sr could be separated effectively without

any contamination from other fission products. It is expected that this encouraging result will lead to the adoption of such a scheme for recovery of ^{90}Sr from ^{99}Mo production waste in the near future.

4.5. PURIFICATION

The most important medical use of ^{90}Y is in the labelling of tumour seeking biomolecules such as monoclonal antibodies and peptides through suitable chelating groups attached to these molecules. These chelators are also capable of binding to metal ions other than Y^{3+} (e.g. Cu^{2+} , Fe^{3+} , Ni^{2+} , Pb^{2+}), and high labelling yield cannot be attained in the presence of such metal ions due to their competitive effect [4.43]. Hence, in addition to high radionuclidic purity and high radioactive concentration, the ^{90}Y product solution used for radiolabelling studies should have very high chemical purity as well. Since impurities present in ^{90}Sr generators can contaminate the ^{90}Y product, it is necessary to use ^{90}Sr recovered from the fission product solution only after thorough purification to remove radioactive and non-radioactive impurities. Many of the recovery schemes discussed above result in a crude ^{90}Sr product that has to be further purified before it can be used in ^{90}Y generators. The different processing schemes used for purification are described below. These schemes are based on the same methods discussed above for the primary separation of ^{90}Sr from fission product mixtures.

4.5.1. Strontium nitrate precipitation

Multicurie quantities of ^{90}Y suitable for therapeutic applications were previously routinely produced at Oak Ridge National Laboratory (ORNL), USA, by separation from ^{90}Sr using an HDEHP/dodecane solvent extraction process that was developed for this purpose [4.44]. The ^{90}Sr feedstock used in the generator in the ORNL process was a purified product derived from $^{90}\text{SrF}_2$ produced during earlier processing of high level waste. The purification was necessary to remove some undesirable trace metal impurities from $^{90}\text{SrF}_2$, including stable Zr resulting from the decay of ^{90}Y . The process was initiated with dissolution of $^{90}\text{SrF}_2$ in nitric acid. Strontium-90 was then precipitated as $\text{Sr}(\text{NO}_3)_2$ using fuming nitric acid, leaving trace metal ions such as Fe and Zr in solution. The precipitate was separated by vacuum filtration and dissolved in 0.1M HCl to prepare the ^{90}Sr generator.

4.5.2. Hydroxide-carbonate precipitation

A production programme for medical grade ^{90}Y is in place at the Pacific Northwest National Laboratory (PNNL), Richland, Washington, USA, based on the abundant supplies of ^{90}Sr separated during earlier campaigns and stored in tanks on the Hanford site [4.45]. Separation of ^{90}Y from ^{90}Sr is carried out from dilute nitric acid solution by the ORNL solvent extraction process using HDEHP/dodecane [4.46]. Before ^{90}Sr solution can be used as feed to the solvent extraction process, it needs purification to remove impurities such as transition metal ions (e.g. Fe^{3+}) and ^{137}Cs , which could contaminate the ^{90}Y product, with deleterious effects. The purification process followed at PNNL is essentially a repetition of the hydroxide-carbonate process used for the initial recovery of ^{90}Sr from high level waste. The ^{90}Sr bearing solution is treated with NaOH to precipitate the hydroxides of transition metal ions. The precipitate is separated by filtration, and Na_2CO_3 is added to the filtrate to precipitate SrCO_3 , leaving ^{137}Cs in solution. The SrCO_3 precipitate is dissolved in acid and the whole process is repeated until the impurities are reduced to undetectable levels.

In a more recent campaign undertaken at PNNL, large scale processing of previously separated, impure ^{90}Sr was carried out to produce 1500 Ci of highly purified ^{90}Sr [4.13]. The ^{90}Sr feedstock was derived from the impure $^{90}\text{SrCO}_3$ product resulting from earlier treatment of stored high level waste using the hydroxide-carbonate process [4.12]. The first step of the purification scheme was dissolution of the carbonate precipitate in nitric acid. Addition of NaOH to this solution to raise the pH to 10 resulted in the precipitation of hydroxides of metal ion impurities (e.g. Fe^{3+} , Y^{3+}). The precipitate was separated by filtration. The filtrate contained 2 Ci/mL ^{90}Sr , and Ca^{2+} was the major impurity, derived from the original HLLW feed. Addition of Na_2CO_3 to the filtrate led to the precipitation of SrCO_3 and CaCO_3 . From analysis of the results it was concluded that about 20% by weight of the precipitate was due to CaCO_3 . The carbonate precipitate was washed with dilute Na_2CO_3 solution, and it was confirmed by analysis that the washing process removed residual ^{137}Cs traces effectively. The measured specific activity of ^{90}Sr was 38 Ci/g. Free from radioactive impurities and deleterious metal ions that could contaminate the ^{90}Y daughter product, this purified ^{90}Sr product was considered sufficient to meet projected market demand for 20–30 years. The ^{90}Sr from PNNL purification is currently used by PerkinElmer to provide the high purity ^{90}Y required for targeted therapy.

4.5.3. Extraction chromatography

The extraction chromatographic process for purification of ^{90}Sr is based on the use of the commercially available Sr-SpecTM resin [4.46]. In this process, a

3M HNO₃ solution of ⁹⁰Sr stock is passed through a Sr-Spec™ resin column. While Sr is retained on the column, impurities including transition metal ions and Zr (from ⁹⁰Y decay) are not retained and pass out of the column. After washing with 3M HNO₃, pure ⁹⁰Sr is stripped using 0.05M HNO₃. Any traces of organic compounds are removed by passing this solution through an Amberlite XAD-7 column. The effluent is purified ⁹⁰Sr product solution, ready to be used for production of ⁹⁰Y. A ⁹⁰Sr purification process based on this resin is part of the flowsheet for production of ⁹⁰Y at POLATOM, Poland [4.47].

4.5.4. Solvent extraction with HDEHP

As noted above, a solvent extraction process using HDEHP in hydrocarbon diluent with TBP as a phase modifier and a lead sulphate carrier precipitation process were used extensively at Hanford, USA, in the 1960s for the initial separation and recovery of a crude ⁹⁰Sr product from high level waste. To meet the demand for a more pure ⁹⁰Sr product for heat source applications, the crude ⁹⁰Sr was subjected to further purification using a modified version of the HDEHP solvent extraction process [4.15, 4.16]. In the modified process, the complexant and buffering agent were different from those used in the initial separation. Although the purity requirement of ⁹⁰Sr for use in production of medical grade ⁹⁰Y is much more stringent, some process details are included here for reference. A chelating agent such as pentasodium diethylenetriaminepentaacetate (Na₅DTPA) was added to the impure ⁹⁰Sr solution to suppress the extraction of metal ion contaminants. The pH of the solution was adjusted to 4.5–5.0 using acetic acid and sodium hydroxide. On contact with the solvent, Sr, Ca and Ce were extracted into the organic phase, leaving all other impurities in the aqueous solution. Strontium was selectively stripped using dilute citric acid. The strip solution was boiled with nitric acid and hydrogen peroxide. A combination of chemical oxidation and radiolysis resulted in destruction of the citric acid. This process was used to produce several megacuries of purified and concentrated ⁹⁰Sr product suitable for heat source applications. In the present context, the quality of this product can be considered as being between the primary crude ⁹⁰Sr product isolated from high level waste and high purity ⁹⁰Sr product suitable for production of medical grade ⁹⁰Y.

4.6. METHODS FOR EVALUATION OF THE QUALITY OF ⁹⁰Sr

As has been mentioned, it is essential that ⁹⁰Sr for use in ⁹⁰Y generator applications be of high purity. After recovery from waste and processing for purification, the ⁹⁰Sr product solution has to be analysed for determination of ⁹⁰Sr

activity and the presence of other radionuclides and metal ion impurities. Some of the methods used for this purpose are briefly described below.

4.6.1. ^{90}Sr activity

The activity of ^{90}Sr in the final product solution can be very high, up to several curies per millilitre. After suitable dilution, the methods commonly employed for measurement of ^{90}Sr in radioactive waste streams and aqueous samples of environmental origin can be used. Such methods involve radiochemical separation of ^{90}Sr from ^{90}Y , followed by beta counting using a Geiger–Müller counter or gas flow proportional counter [4.9]. The procedures used for radiochemical separation include some of the methods discussed above for production scale processing of waste streams for recovery of ^{90}Sr . One widely used precipitation scavenging procedure involves the following steps:

- (1) Precipitation of $\text{Sr}(\text{NO}_3)_2$ with fuming HNO_3 ;
- (2) Dissolution of $\text{Sr}(\text{NO}_3)_2$ in water;
- (3) Scavenging of Y by precipitation of $\text{Fe}(\text{OH})_3$ with ammonium hydroxide;
- (4) Precipitation of SrCO_3 , followed by counting.

Any ^{89}Sr present in the solution also follows ^{90}Sr in the separation procedure and contributes to the β^- activity measured. As previously noted, ^{89}Sr contamination can be eliminated by ageing the waste for a suitable period before recovery of ^{90}Sr . Nevertheless, it is necessary to ensure that ^{89}Sr either is not present or is present only at extremely low concentrations. This can be done by allowing ^{90}Y to grow to secular equilibrium, followed by separation from $^{89}\text{Sr}/^{90}\text{Sr}$ as $\text{Y}(\text{OH})_3$ by adding Y carrier and ammonium hydroxide. For beta counting, the hydroxide is dissolved in acid and Y is precipitated as the oxalate. The measured activity of ^{90}Y is equal to the activity of ^{90}Sr and can be subtracted from the total Sr activity to obtain the activity of ^{89}Sr .

The use of liquid scintillation counting (LSC) is also becoming popular for measuring ^{89}Sr , ^{90}Sr and ^{90}Y [4.48]. After separation of Sr, measurement in the Cerenkov counting mode without any cocktail gives ^{89}Sr ($E_{\beta\text{max}}$: 1.49 MeV) activity with a negligible contribution from ^{90}Sr ($E_{\beta\text{max}}$: 0.546 MeV) because of its low beta energy. Addition of a cocktail and counting in the liquid scintillation mode gives a measure of the total radiostrontium activity. The contribution of ingrowing ^{90}Y ($E_{\beta\text{max}}$: 2.28 MeV) can be accounted for either by calculation or by Cerenkov counting. In recent times, extraction chromatography using Sr-SpecTM resin has also become very popular as a fast, convenient method for the primary separation of radiostrontium from other radiochemical impurities before analysis [4.37, 4.49, 4.50].

Extraction paper chromatography (EPC) can also be used for separation of ^{90}Y from ^{90}Sr prior to quantification [4.51]. In this technique a ^{90}Y specific chelate, KSM 17 (2-ethyl hexyl 2-ethyl hexyl phosphonic acid), is impregnated at the point of spotting on a chromatography paper to be used for separation of Sr and Y. The $^{90}\text{Sr}/^{90}\text{Y}$ mixture is applied to the chelate spot and chromatography is performed in a suitable solvent, such as saline. The chromatography offers a clean separation of ^{90}Y and ^{90}Sr . The ^{90}Sr that migrates to the solvent front can be estimated by LSC and compared with the total activity spotted on the paper. This method, primarily developed for estimation of ^{90}Sr impurities in ^{90}Y , can also be adapted for radiochemical separation and quantification of ^{90}Sr .

4.6.2. Other radionuclides

In view of the high activities of several gamma emitting fission products in the original waste solution, it is possible that the final ^{90}Sr product will contain traces of some of these radionuclides (e.g. ^{137}Cs (E_γ : 0.662 MeV), $^{106}\text{Ru}/^{106}\text{Rh}$ (E_γ : 0.523, 0.624 MeV)). The presence of gamma emitters in the ^{90}Sr product can be determined by subjecting a suitably diluted sample to high resolution gamma spectrometry. A high performance germanium (HPGe) detector coupled to an 8K multichannel analyser is commonly used for this purpose.

4.6.3. Metal ion impurities

It is possible for metal ions present in the original waste and impurities present in the processing chemicals to find their way into the final product. Some of these metal ions can contaminate the ^{90}Y milked from the generator and interfere with subsequent labelling of bioactive molecules. The concentration of metal ion impurities can be conveniently determined using inductively coupled plasma atomic emission spectroscopy (ICP-AES).

4.7. CONCLUSION

An assured supply of high purity ^{90}Sr in adequate quantities is essential for realizing the benefits of ^{90}Y in therapeutic applications. A product of ^{235}U fission, ^{90}Sr is generated annually in quantities equivalent to hundreds of megacuries during irradiation of U in reactors all over the world. Compared with the amount produced, the quantity of ^{90}Sr required for ^{90}Y generator applications is very small. The long half-life of ^{90}Sr (~28 a) also ensures that, once procured, this parent radioisotope can be used for repeated milking of ^{90}Y for many years. In

fact, a supply of a few tens of kilocuries of high purity ^{90}Sr is considered more than adequate to meet present as well as anticipated future requirements.

HLLW from the reprocessing of spent nuclear fuel is the primary resource for recovery of ^{90}Sr . However, this resource is available only to a few countries. With the necessary technological infrastructure for the handling and processing of this highly radioactive waste already in place, it is relatively easy for these countries to implement a ^{90}Sr separation flowsheet in their facilities. In fact, large scale separation of ^{90}Sr was carried out in the past in the USA for the purpose of making radioisotope thermoelectric generators and as part of overall waste management schemes. An industrial facility for the recovery of ^{90}Sr and other radioisotopes from HLLW is currently in operation in the Russian Federation. The current world supply of ^{90}Sr comes from these two countries. It would not be too difficult for other countries having reprocessing programmes to set up facilities for recovery of ^{90}Sr from HLLW. Since the ^{90}Sr requirements are not very high, even campaign mode operation to recover a few kilocuries would be adequate.

Another relatively modest resource is the waste from production of ^{99}Mo by neutron induced fission of ^{235}U . In the absence of HLLW from reprocessing, this resource can also be exploited for the recovery of ^{90}Sr in multicurie quantities to meet local requirements.

A number of mature process technologies are available for the separation and purification of ^{90}Sr from waste streams. Operating experience exists using precipitation, ion exchange and solvent extraction flowsheets for the recovery of ^{90}Sr in multi-megacurie quantities. Extraction chromatography is a relatively new technique that is very promising. Selection of the most suitable process to be adopted in any recovery programme depends on a number of factors (e.g. scale of operation, availability of solvents and reagents, management of secondary wastes). The primary separation of ^{90}Sr has to be followed by further processing for purification to meet the quality standards if the product has to be used for ^{90}Y generator applications. Hence the purification step should be integrated into the overall recovery scheme. This also calls for a reliable programme and facilities for ascertaining product quality.

Strontium-90 is commercially available at present and hopefully will continue to be available in adequate quantities in the future as well. However, there currently are only a few suppliers. A review and assessment of the available information on process technology shows that it would not be very difficult to implement ^{90}Sr recovery programmes at more centres and thus widen the supply base of this important radioisotope.

ACKNOWLEDGEMENTS

The author gratefully acknowledges the support and encouragement from S.D. Misra, Director of the Nuclear Recycle Group, BARC, in the preparation of this review article.

REFERENCES TO CHAPTER 4

- [4.1] GOLDENBERG, D.M., Targeted therapy of cancer with radiolabeled antibodies, *J. Nucl. Med.* **43** (2002) 693–713.
- [4.2] VERIN, V., et al., Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty, *N. Engl. J. Med.* **344** 4 (2001) 243–249.
- [4.3] PANDEY, U., et al., Evaluation of ^{90}Y -DTPA and ^{90}Y -DOTA for potential application in intra-vascular radionuclide therapy, *Appl. Radiat. Isot.* **57** (2002) 313.
- [4.4] PANDEY, U., MUKHERJEE, A., CHAUDHARY, P.R., PILLAI, M.R.A., VENKATESH, M., Preparation and studies with ^{90}Y -labeled particles for use in radiation synovectomy, *Appl. Radiat. Isot.* **55** (2001) 471.
- [4.5] KAMPEN, W.U., VOTH, M., PINKERT, J., KRAUSE, A., Therapeutic status of radiosynoviorthesis of the knee with yttrium [^{90}Y] colloid in rheumatoid arthritis and related indications, *Rheumatology* **46** 1 (2007) 16–24.
- [4.6] SCHULZ, L.A., BRAY, L.A., Solvent extraction recovery of byproduct ^{137}Cs and ^{90}Sr from HNO_3 solutions – A technology review and assessment, *Sep. Sci. Technol.* **22** 2&3 (1987) 191–214.
- [4.7] INTERNATIONAL ATOMIC ENERGY AGENCY, Feasibility of Separation and Utilization of Caesium and Strontium from High Level Liquid Waste, Technical Reports Series No. 356, IAEA, Vienna (1993).
- [4.8] ORTH, R.J., KURATH, D.E., Review and assessment of technologies for the separation of strontium from alkaline and acidic media, Rep. PNL-9053, Pacific Northwest National Laboratory, Richland, WA, USA (1994).
- [4.9] SUNDERMAN, D.N., TOWNLEY, C.W., The radiochemistry of barium, calcium and strontium, NAS-NS-3010, National Research Council, Washington, DC (1960).
- [4.10] BEARD, S.J., SWIFT, W.H., Strontium-90: Recovery and lag storage interim program, Rep. HW-66297, US DOE, Washington, DC (1960).
- [4.11] DEPARTMENT OF ENERGY, The 324 building radiochemical engineering cells and high-level vault closure plan, Rep. DOE/RL-96-73, US DOE, Washington, DC (1977).
- [4.12] HOSAKA, T.Y., SEVIGNY, G.J., SCHLENDER, M.H., High level liquid waste treatment process: Reducing risk and capitalizing on high value isotopes, *Proc. Waste Management Spectrum '96*, Seattle 1996, American Nuclear Society, Washington, DC (1996) 2257–2260.
- [4.13] WESTER, D.W., et al., Large-scale purification of ^{90}Sr from nuclear waste materials for production of ^{90}Y , a therapeutic medical radioisotope, *Appl. Radiat. Isot.* **59** (2003) 35–41.
- [4.14] INTERNATIONAL ATOMIC ENERGY AGENCY, Management of Radioactive Waste from ^{99}Mo Production, IAEA-TECDOC-1051, IAEA, Vienna (1998).

- [4.15] BEARD, S.J., MOORE, R.L., “Large-scale recovery and purification of fission products”, *Progress in Nuclear Energy (Series III), Process Chemistry*, Vol. 4 (STEVENSON, C.E., MASON, E.A., GRESKY, A.T., Eds), Pergamon Press, London (1969) 645–667.
- [4.16] BUCKINGHAM, J.S. (Ed.), *Waste Management Technical Manual*, ISO-100, ISOICHEM Inc., Richland, WA (1967).
- [4.17] RAMANUJAM, A., et al., Separation of ^{90}Sr from PUREX high level waste and development of a ^{90}Sr - ^{90}Y generator, Rep. BARC/2000/E/009, Bhabha Atomic Research Centre, Mumbai (2000).
- [4.18] RAMANUJAM, A., et al., Separation of carrier-free ^{90}Y from high level waste by supported liquid membrane using KSM-17, *J. Radioanal. Nucl. Chem.* **247** 1 (2001) 185.
- [4.19] DHAMI, P.S., et al., Studies on the development of a two stage supported liquid membrane system for the separation of carrier-free ^{90}Y using KSM-17 and CMPO as carriers, *Sep. Sci. Technol.* **42** (2007) 1107–1121.
- [4.20] CHAKRAVARTY, R., et al., Development of an electrochemical ^{90}Sr - ^{90}Y generator for separation of ^{90}Y suitable for targeted therapy, *Nucl. Med. Biol.* **35** (2008) 245–253.
- [4.21] HEALY, T.V., CARTER, P.E., BROWN, P.E., The extraction of strontium from fission product solutions, *Progress in Nuclear Energy (Series III), Process Chemistry*, Vol. 1 (BRUCE, F.R., FLETCHER, J.M., HYMAN, H.H., KATZ, J.J., Eds), Pergamon Press, London (1956) 363–368.
- [4.22] BRAY, L.A., et al., The recovery and purification of multi-kilocurie quantities of fission product strontium by cation exchange, Rep. HW-70998, Hanford Atomic Products Operation, Richland, WA (1961).
- [4.23] WHEELWRIGHT, E.J., “A generic ion-exchange process for the recovery and purification of valuable elements from the nuclear industry”, *Ion Exchange in the Process Industries*, Society of Chemical Industry, London (1970) 202–208.
- [4.24] HORWITZ, E.P., DIETZ, M.L., FISHER, D.E., SREX: A new process for the extraction and recovery of strontium from acidic nuclear waste streams, *Solv. Extr. Ion Exch.* **9** 1 (1991) 1–25.
- [4.25] LUMETTA, G.J., WAGNER, M.J., JONES, E.O., Separation of strontium-90 from Hanford high-level radioactive waste, *Sep. Sci. Technol.* **30** 7–9 (1995) 1087–1101.
- [4.26] DIETZ, M.L., HORWITZ, E.P., ROGERS, R.D., Extraction of strontium from acidic nitrate media using a modified PUREX solvent, *Solv. Extr. Ion Exch.* **13** 1 (1995) 1–17.
- [4.27] ROMANOVSKY, V.N., “R&D activities on partitioning in Russia”, Fifth OECD/NEA Inf. Exchange Mtg on Actinide and Fission Product Partitioning and Transmutation, SCK•CEN, Mol, Belgium, 1998.
- [4.28] COTTON, F.A., WILKINSON, G., GAUS, P.L., *Basic inorganic chemistry*, 3rd edn, John Wiley and Sons, Chichester (2004) 338–342.
- [4.29] RAIS, J., SELUCKY, P., KYRS, M., in *J. Inorg. Nucl. Chem.* **38** (1976) 1376.
- [4.30] SELUCKY, P., VANURA, P., RAIS, J., KYRS, M., Rapid method for the separation of Sr-90 for its determination in a mixture with long-lived fission products, *Radiochem. Radioanal. Lett.* **38** 4 (1979) 297–302.
- [4.31] HERBST, R.S., et al., Development and testing of a cobalt dicarbollide based solvent extraction process for the separation of cesium and strontium from acidic tank waste, *Sep. Sci. Technol.* **37** 8 (2002) 1807–1831.

- [4.32] ESIMANTOVSKI, V.N., et al., Technological tests of HAW partitioning with the use of chlorinated cobalt dicarbollide: Management of secondary waste, Proc. Symp. Waste Management, Tucson 1992, University of Arizona (1992) 801–804.
- [4.33] ROMANOVSKY, V.N., “Management of accumulated high level waste at the Mayak Production Association in the Russian Federation”, Issues and Trends in Radioactive Waste Management (Proc. Int. Conf. Vienna, 2003), IAEA, Vienna (2003) 360.
- [4.34] ROMANOVSKY, V.N., “US-Russian cooperative program in research and development of chemical separation technologies”, Chemical Separations in Nuclear Waste Management: The State of the Art and a Look to the Future (CHOPPIN, G.C., KHANKHASAYEV, M., PLENDL, H.S., Eds), Rep. DOE/EM-0591, Battelle, Columbus (2001) 57–66.
- [4.35] HERBST, R.S., et al., Development of the universal extraction (UNEX) process for the simultaneous recovery of Cs, Sr and actinides from acidic radioactive wastes, Sep. Sci. Technol. **38** 12&13 (2003) 2685.
- [4.36] ROMANOVSKY, V.N., et al., “UNEX process — State of the art and outlook”, Proc. GLOBAL 2005 Int. Conf. Nuclear Energy System for Future Generation and Global Sustainability, Tsukuba (2005).
- [4.37] HORWITZ, E.P., DIETZ, M.L., FISHER, D.E., Separation and preconcentration of strontium from biological, environmental and nuclear waste samples by extraction chromatography, Anal. Chem. **63** (1991) 522–525.
- [4.38] HORWITZ, E.P., CHIARIZIA, R., DIETZ, M.L., A novel strontium-selective extraction chromatographic resin, Solv. Extr. Ion Exch. **10** 2 (1992) 313–336.
- [4.39] LUMETTA, G.J., SWANSON, J.L., BRAY, L.A., Radionuclide separations for the reduction of high-level waste volume, Rep. PNL-SA-21389, Pacific Northwest Laboratory, Richland, WA (1993).
- [4.40] LUMETTA, G.J., WESTER, D.W., MORREY, J.R., WAGNER, M.J., Preliminary evaluation of chromatographic techniques for the separation of radionuclides from high-level radioactive waste, Solv. Extr. Ion Exch. **11** 4 (1993) 663–682.
- [4.41] SHAPOVALOV, V.V., KANYGIN, V.V., NARYSHKIN, A.G., NEROZIN, N.A., SMETANIN, E.Y., Extraction-chromatographic recovery of ^{90}Sr from spent nuclear fuel, Radiochemistry **48** 1 (2006) 53–54.
- [4.42] FORNACIARI, M.C., FURNARI, J.C., COHEN, I.M., Considerations on the ^{90}Sr recovery as part of a process for ^{90}Mo production from LEU fission, Int. Mtg Reduced Enrichment for Research and Test Reactors, Bariloche, Argentina, 2002, Argonne National Laboratory, Argonne, IL (2002).
- [4.43] MIKOLAJCZAK, R., PARUS, J.L., Reactor produced beta-emitting nuclides for nuclear medicine, World J. Nucl. Med. **4** 3 (2005) 184–190.
- [4.44] WIKE, J.S., GUYER, C.E., RAMEY, D.W., PHILLIPS, B.P., Chemistry for commercial scale production of yttrium-90 for medical research, Appl. Radiat. Isot. **41** 9 (1990) 861–865.
- [4.45] BRAY, L.A., et al., Production of ^{90}Y at Hanford, Radioact. Radiochem. **3** 4 (1992) 22–24.
- [4.46] DIETZ, M.L., HORWITZ, E.P., Improved chemistry for the production of yttrium-90 for medical applications, Appl. Radiat. Isot. **43** 9 (1992) 1093–1101.

- [4.47] MIKOLAJCZAK, R., CHRUSTOWSKI, K., ZELEK, Z., KARCZMARCZYK, U., SAWLEWICZ, K., Development of radionuclide generator technologies for therapeutic radionuclides: Current status at RC POLATOM-Poland, in Rep. 1st Research Coord. Mtg Development of Generator Technologies for Therapeutic Radionuclides, Vienna, 2004, IAEA, Vienna (2004) 90–95.
- [4.48] L'ANNUNZIATA, M.F. (Ed.), Handbook of Radioactivity Analysis, 2nd edn, Academic Press, San Diego, CA (2003).
- [4.49] FAJARDO, Y., et al., Multisyringe flow injection analysis of stable and radioactive strontium in samples of environmental interest, *Appl. Radiat. Isotop.* **61** 2–3 (2004) 273–277.
- [4.50] JAKOPIC, R., BENEDIK, L., Tracer studies on Sr resin and determination of ^{90}Sr in environmental samples, *Acta Chim. Slov.* **52** 3 (2005) 297–302.
- [4.51] PANDEY, U., DHAMI, P.S., JAGESIA, P., VENKATESH, M., PILLAI, M.R.A., A novel extraction paper chromatography (EPC) technique for the radionuclidic purity evaluation of ^{90}Y for clinical use, *Anal. Chem.* **80** (2008) 801–807.

Chapter 5

REACTOR PRODUCTION AND PROCESSING OF ^{188}W

F.F. KNAPP, Jr., S. MIRZADEH
Nuclear Medicine Program,
Isotope Development Group,
Oak Ridge National Laboratory (ORNL),
Oak Ridge, Tennessee,
United States of America

M. GARLAND
Process Engineering Research Group,
Nuclear Science and Technology Division,
Oak Ridge National Laboratory (ORNL),
Oak Ridge, Tennessee,
United States of America

B. PONSARD
SCK•CEN, BR2 Reactor,
Boeretang, Belgium

R. KUZNETSOV
Federal State Unitary Enterprise
“State Scientific Centre of the Russian Federation”,
Research Institute of Atomic Reactors (RIAR),
Dimitrovgrad, Russian Federation

5.1. INTRODUCTION

The increasing use of unsealed radioactive targeting agents for cancer treatment and other therapeutic applications requires routine availability of cost effective radioisotopes. Reactor produced ^{188}W ($T_{1/2}$: 69 d) decays to ^{188}Re , which is a key example of a high energy beta emitting therapeutic radioisotope that is readily available in no-carrier-added form from the alumina based $^{188}\text{W}/^{188}\text{Re}$ ($T_{1/2}$: 16.9 h) generator system [5.1–5.6]. Rhenium-188 has many attractive properties for a wide variety of therapeutic applications, including emission of a high energy beta particle with a maximum energy of 2.12 MeV, a 155 keV (15%) gamma photon for imaging, and versatile chemistry for attachment to a variety of targeting molecules. These properties make ^{188}Re an important candidate for

applications where deep tissue penetration is a benefit. Emission of gamma photons which can be readily imaged is an added benefit that permits evaluation of biodistribution, pharmacokinetics and dosimetry. The long parent half-life and consistent excellent generator performance result in a useful shelf-life of several months [5.3–5.5]. The 24 h post-generator ^{188}Re elution in-growth of 62% and high elution yields (75–85%) result in daily yields of about 50%, with consistently low ^{188}W parent breakthrough ($<10^{-6}$). Simple post-elution concentration methods have been developed to provide very high specific volume solutions of ^{188}Re for radiolabelling (>700 mCi/mL saline from a 1 Ci generator) [5.3–5.7].

5.2. BACKGROUND

A variety of ^{188}Re labelled therapeutic radiopharmaceuticals and devices have been developed, and a large number of physician sponsored clinical trials with applications in nuclear medicine, oncology and interventional cardiology/radiology are currently in progress throughout the world [5.1–5.5]. One important application is palliation of metastatic bone pain with ^{188}Re -HEDP, which is readily prepared from a simple ‘kit’ [5.7–5.10] and is a cost effective alternative to other available agents, especially in developing regions. One important recent study has demonstrated enhancement of the progression-free interval and survival time by repeated ^{188}Re -HEDP injections [5.7]. The results of these important studies have demonstrated that this agent is not only useful for pain palliation, but also elicits a therapeutic effect. Post-percutaneous transluminal coronary angioplasty (PTCA) treatment of arterial segments using liquid filled balloons with ^{188}Re perrhenate or MAG_3 is an effective and cost effective approach to uniform vessel wall dose delivery for inhibition of hyperplasia [5.11–5.16]. Other clinical applications of ^{188}Re include the use of the ^{188}Re labelled anti-NCA95 (CD66) antibody in conjunction with external beam irradiation as an effective method of myeloablation/conditioning prior to stem cell transplantation in leukaemia patients [5.17–5.20]. In addition, the ^{188}Re -P2045 peptide has been developed and initial clinical evaluation has demonstrated targeting of small cell/non-small-cell lung tumours [5.20], and ^{188}Re labelled antibodies are being evaluated for tumour therapy. Therapy of refractory liver cancer has been shown as a particularly effective strategy using site specific catheter delivery of the ^{188}Re -HDD-Lipiodol agent to primary and metastatic liver tumours [5.21–5.28] and is being used in several countries and in an IAEA sponsored multicentre trial [5.28]. In addition, ^{188}Re labelled B20 albumin particles [5.29] and the ^{188}Re -DEDIC agent [5.30] have been used for the same application. Particularly in the developing world, the use of no-carrier-

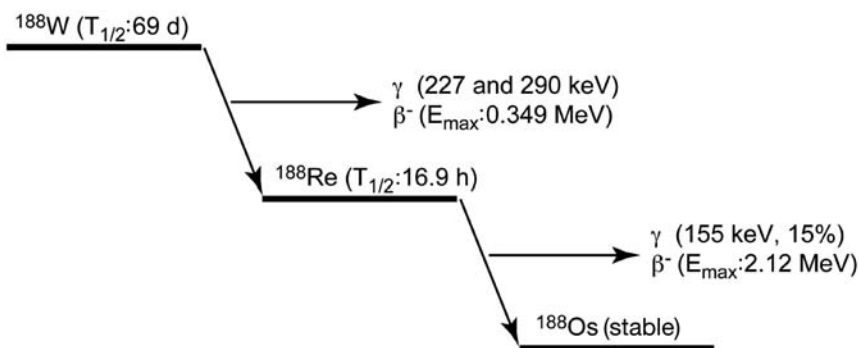


FIG. 5.1. Principal emissions relevant to the decay scheme of ^{188}W .

added ^{188}Re available from the $^{188}\text{W}/^{188}\text{Re}$ generator has proved to be a convenient and cost effective system to provide this important therapeutic radioisotope. Use of the $^{188}\text{W}/^{188}\text{Re}$ generator in a centralized radiopharmacy would be expected to optimize the costs and use of ^{188}Re .

5.3. NUCLEAR DECAY

The principal decay of ^{188}W is shown in Fig. 5.1. The 69 d half-life of ^{188}W provides a generator system for useful on-demand routine availability of no-carrier-added ^{188}Re . The high energy beta emission and principal gamma photon emission result from decay of ^{188}Re to stable ^{188}Os .

5.4. PRODUCTION AND PROCESSING

5.4.1. Reactor production of ^{188}W

Tungsten-188 is a key example where very high thermal flux is required for production of sufficient specific activity for practical use for the adsorption based $^{188}\text{W}/^{188}\text{Re}$ generator [5.31–5.37]. As a consequence of the double neutron production process, modest thermal cross-section values (Table 5.1) and product burnup, the ^{188}W is reactor produced with relatively low specific activity [5.34]. For example, 24 d irradiation even at the high thermal flux of $>10^{15}$ neutrons \cdot $\text{cm}^{-2} \cdot \text{s}^{-1}$ yields ^{188}W with a specific activity of only 4–5 Ci/g [5.33]. Use of this relatively low specific activity ^{188}W requires larger amounts of alumina for the generator column, thus increasing the eluent volume and decreasing the ^{188}Re concentration (activity/volume (mCi/mL)) [5.3–5.5]. The increase in specific

TABLE 5.1. EXAMPLES OF NUCLEAR CONSTANTS FOR NUCLIDES IN THE ^{188}W PRODUCTION CHAIN
(from RIAR)

Nuclide	Decay constant, λ (s^{-1})	Cross-section, σ (b)	Values for resonance integral, I (b)
^{186}W	—	37.9	485
^{187}W	8.09×10^{-6}	64.0	2760; 10
^{188}W	1.16×10^{-7}	12	0; 50 000; 1.4
^{187}Re	—	76.4	300
^{188}Re	1.13×10^{-5}	<2	—

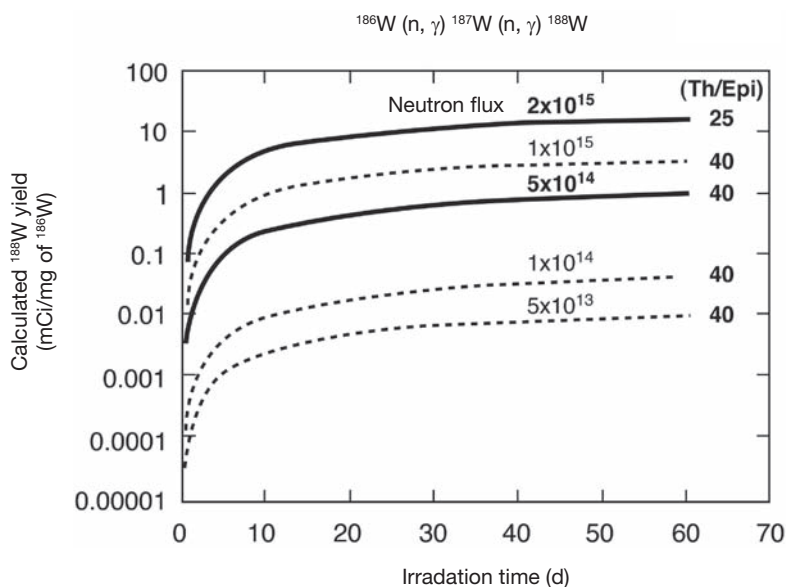


FIG 5.2. Production of ^{188}W as a function of thermal neutron flux (values estimated using the ORNL LAURA code using unpublished cross-section data).

activity using very high flux reactors is dramatically illustrated for the production of ^{188}W from enriched ^{186}W by the $^{186}\text{W}(n,\gamma)^{187}\text{W}(n,\gamma)^{188}\text{W}$ pathway (Fig. 5.2). The modest ^{186}W and ^{187}W neutron capture cross-sections (Fig. 5.3), the competing burnup of the ^{188}W product [5.36] and the significant self-shielding that has been observed [5.34, 5.35] are factors that decrease the ^{188}W specific activity. At the ORNL High Flux Isotope Reactor (HFIR), production of ^{188}W

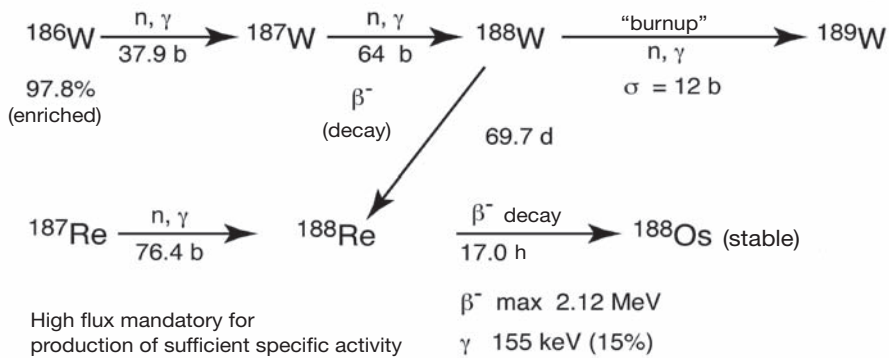


FIG. 5.3. Scheme for reactor production of ^{188}W .

from both enriched ^{186}W metal and tungsten oxide targets has been evaluated over the past several years [5.31–5.35].

5.4.2. Processing of ^{188}W

The metallic powder targets are usually processed by oxidation with hydrogen peroxide and/or hypochlorite in the presence of base, and oxide targets are dissolved in base with concomitant oxidation [5.33]. The reactor production yields of ^{188}W are about one order of magnitude lower than the calculated values for the $^{186}\text{W}(n,\gamma)^{187}\text{W}$ ($\sigma: 37.9 \pm 0.6 \text{ b}$) and $^{186}\text{W}(n,\gamma)^{188}\text{W}$ ($\sigma: 64 \pm 10 \text{ b}$) reactions. The neutron burnup cross-section for the $^{188}\text{W}(n,\gamma)^{189}\text{W}$ nuclear reaction is one factor that recently has been shown to contribute to the reduced production yields observed for ^{188}W [5.36]. By irradiation of ^{188}W , a value of $12.0 \pm 2.5 \text{ b}$ has been calculated for this neutron burnup cross-section.

5.4.3. Availability of enriched ^{186}W target material

Ideally, ^{188}W should be produced by neutron irradiation of enriched ^{186}W targets, especially for the subsequent preparation of high activity $^{188}\text{W}/^{188}\text{Re}$ generators. The use of enriched targets is also required to minimize co-production of other radioactive species. In addition, the use of enriched targets reduces the target volume considerably, since the W targets are quite large because of the modest ^{188}W production yields. Furthermore, because of the relatively low specific activity of ^{188}W produced by the double neutron capture process, even at very high thermal flux, the highest specific activity ^{188}W is generally sought to minimize the amount of adsorbent required for loading of the traditional aluminium oxide adsorption type generator.

Highly enriched ^{186}W is available from several sources, and the current costs are about US \$1/mg of >95% enriched ^{186}W (e.g. ORNL Stable Isotope Inventory). The irradiation of high purity natural W has also been evaluated but results in much lower specific activity and requires even higher levels of the alumina adsorbent [5.37].

Although large electromagnetically separated quantities of highly enriched ^{186}W are available on the world market and centrifuge enrichment has also been demonstrated on a small scale, another strategy that has been demonstrated is the recovery of non-activated ^{186}W from used generators, since only a small fraction of ^{186}W is transmuted to ^{188}W during the reactor irradiation process. By increasing the pH of the generator eluent, salts of tungstic acid can be readily removed [5.38]. The use of ammonium hydroxide with peroxide, for instance, can remove >95% of the available W from the alumina column. Subsequent precipitation with nitric acid (chloride complexes have limited solubility), recovery by centrifugation and then heating at high temperature readily converts the W to the oxide, which could then conceivably be used for preparation of additional targets for neutron irradiation. Although long decay periods would be expected to reduce the activity of the residual radioactivity to manageable levels, this recovered W would still be radioactive with longer lived contaminants. Target fabrication with this material would thus probably require special handling. Nonetheless, this approach could represent a possible method for recovery of the ^{186}W target material.

5.4.4. Target design/requirements and preparation

As has been described, ^{188}W is reactor produced by double neutron capture on ^{186}W , and enriched ^{186}W is the preferred target material to minimize the co-production of other radioactive species that require increased shielding (i.e. ^{185}W from neutron capture on ^{184}W) and to optimize the ^{188}W activity produced/target mass. The use of powder targets consisting of W metal or tungsten oxide or pressed/sintered metallic targets for production of ^{188}W is reviewed in this section.

5.4.4.1. ORNL High Flux Isotope Reactor (HFIR)

The use of either granular/powder ^{186}W enriched metallic or oxide targets has already been described. Another strategy currently used at ORNL [5.37] involves the use of enriched metallic ^{186}W targets that are pressed into pellets and subsequently sintered at high temperature prior to neutron irradiation. This approach dramatically increases the target density and thus the loading and ^{188}W production capability per target, and about 5 g of these discs (8–10/target) can be

loaded into one HFIR hydraulic tube target assembly. The issue of self-shielding may need to be taken into account, as this decreases the specific activity compared with the use of granular/powder targets [5.34]. Although the total ^{188}W activity produced per target is higher with the pressed targets, since significantly more target material can be used per target holder, the ^{188}W specific activity decreases as the mass of the enriched ^{186}W increases. Although the factors that result in this discrepancy are not fully elucidated or understood, the specific activity of the irradiated enriched ^{186}W pellets is considerably less (20–25%) than the specific activity of the irradiated granular/powder enriched ^{186}W target [5.33].

5.4.4.2. *SM reactor, RIAR, Dimitrovgrad, Russian Federation*

At the SM reactor, enriched ^{186}W metal oxide powder targets are encased in sealed quartz tubes, and these primary tubes are then encased in the irradiation vessels.

5.4.5. **Estimated production yields and deviation from theoretical calculations**

The calculated specific activity values of ^{188}W as a function of thermal neutron flux are shown in Fig. 5.2, which demonstrates a dramatic increase in specific activity with increasing thermal neutron flux. From a practical perspective, a minimal thermal neutron flux of $\sim 1 \times 10^{15}$ neutrons \cdot cm $^{-2}$ \cdot sec $^{-1}$ is required to produce a specific activity of about 1 Ci ^{188}W /g of ^{186}W , adequate for preparation of an alumina based generator. Figure 5.4 shows the production values of ^{188}W in the ORNL HFIR and the deviation from the theoretical values by a factor of 2–4. These data, accumulated over several years, also illustrate the higher specific activities obtained by processing of the irradiated enriched ^{186}W oxide targets compared with the metal targets, although the reasons for this aberration are not apparent.

5.4.6. **Importance of thermal neutron flux for reactor production of ^{188}W**

For practical reasons, if ^{188}W is required for the fabrication of high activity traditional alumina based adsorption type $^{188}\text{W}/^{188}\text{Re}$ generators, a minimal thermal flux of about 1×10^{15} neutrons \cdot cm $^{-2}$ \cdot sec $^{-1}$ is required for production of ^{188}W with a minimum specific activity of about 1 mCi per milligram of W. This estimate is based on several factors, including the double neutron capture production pathway, from which yields are a function of the square of the thermal flux. In addition, the target volume restrictions of some reactors can be a factor,

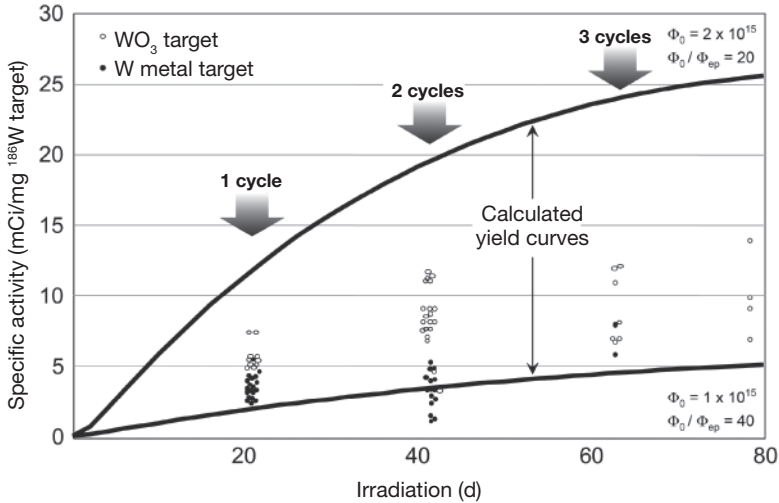


FIG 5.4. Production of ¹⁸⁸W in the ORNL HFIR from irradiation of ¹⁸⁶W enriched metallic and oxide targets compared with theoretical production yields [5.33].

especially in high flux positions. Another requirement is minimization of the W mass loading on the ¹⁸⁸W/¹⁸⁸Re generator adsorbent in order to minimize the volume of saline eluant to optimize the specific volume (defined here as activity/unit volume) of the ¹⁸⁸Re eluted. Thus, a balance is required between the target size, required specific activity, mass of aluminium oxide and required specific volume of the ¹⁸⁸Re bolus.

5.4.7. Self-shielding of thick targets

Although the use of pressed/sintered metallic enriched ¹⁸⁶W targets has been described and such targets are now used at ORNL for routine production of ¹⁸⁸W, the use of these dense targets results in apparent significant self-shielding and thus depressed ¹⁸⁸W yields per unit mass of W. The ramifications of the use of such targets on the ¹⁸⁸W yields have been examined in detail [5.36]. Recent studies have evaluated the factors that contribute to the decrease in ¹⁸⁸W specific activity from both experimental and theoretical perspectives [5.34]. Both neutron self-shielding and temperature effects were characterized, to develop a strategy for design of a W target that would optimize ¹⁸⁸W production yield.

For these studies, five concentric W cylinders formed the target assembly (6 mm in diameter × 20 mm), which was irradiated in the ORNL HFIR. Following discharge, the target was disassembled and the radioactive species (i.e. ¹⁸⁷W and ¹⁸⁸W) in each target component were analysed. From these analyses, it

was determined that the decrease in ^{188}W yield resulted from depletion of epithermal neutrons at resonant energies, which was most significant within the initial 0.4 mm depth of the target bundle. The results of these studies further illustrated that the ^{188}W yield at the centre of the target bundle (i.e. beyond the 0.4 mm depth; the tungsten rod) does not decrease, as would have been expected due to neutron attenuation. This observation was explained by the elevated temperatures in the target interior, which result in an increase in the ^{188}W yield through Doppler broadening of cross-sections, which then compensates for the reduced ^{188}W yield resulting from neutron attenuation. The results of these studies have also demonstrated the apparent inaccuracy of the published thermal cross-section for ^{187}W [5.34]. To evaluate the practical implications of these observations, ‘donut’ configuration targets were prepared by pressing and sintering enriched ^{186}W . Initial irradiation of a set of these targets has been completed in the ORNL HFIR, and processing and analysis is currently in progress to evaluate if the overall specific activity of ^{188}W produced from such a donut target design exceeds the specific activity of similar pressed/sintered disc type targets.

5.5. CHEMICAL ASPECTS

5.5.1. Neutron-induced co-production of radionuclide impurities

During neutron irradiation of enriched ^{186}W the co-production of radionuclide impurities cannot be avoided, and both ^{191}Os and ^{192}Ir are produced in varying amounts [5.4–5.6] depending on the neutron flux characteristics and other irradiation parameters. Although not yet documented in detail, we assume that these two impurities are co-produced by the series of transformations summarized in Fig. 5.5.

5.5.2. Importance of ^{188}W backup production capabilities

Because of the predictable and unpredictable issues associated with reactor maintenance, refuelling, upgrades and compliance, it is important to have backup production capabilities for all reactor produced radioisotopes. This is particularly true for the production of ^{188}W , which requires long irradiation periods. Table 5.2 summarizes those reactors with sufficiently high thermal neutron flux that have been used for production of ^{188}W having sufficient specific activity for preparation of adsorption type $^{188}\text{W}/^{188}\text{Re}$ generators.

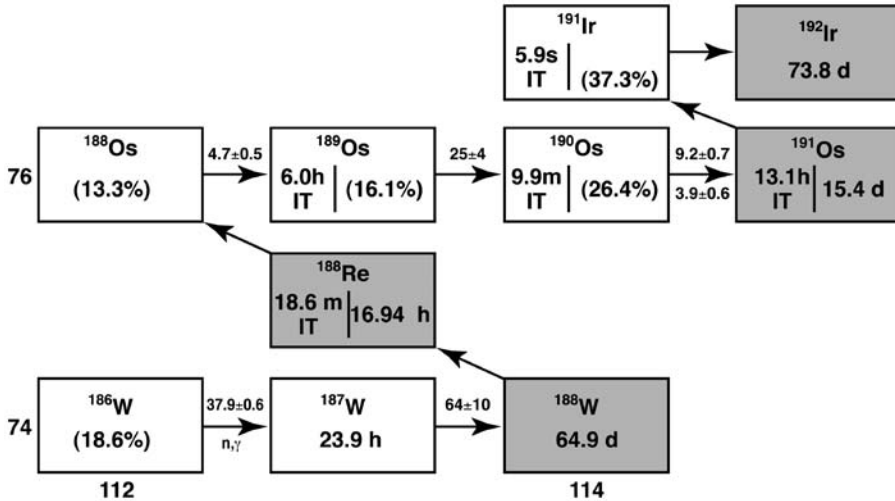


FIG 5.5. Possible pathways for formation of ^{191}Os and ^{192}Ir radionuclide impurities detected in ^{188}W produced by neutron irradiation of enriched ^{186}W .

TABLE 5.2. EXAMPLES OF HIGH FLUX RESEARCH REACTORS FOR THE PRODUCTION OF ^{188}W

Reactor	Institution	Reported/projected specific activity (Ci $^{188}\text{W}/\text{g W}$)	Comment/web site information
HFIR	ORNL, Oak Ridge, USA	4–5 Ci, one cycle 8–9 Ci, two consecutive cycles	Routine production since 1986 http://www.ornl.gov/sci/nuclear_science_technology/nu_med/
SM3	Research Institute for Atomic Reactors (RIAR), Dimitrograd, Russian Federation	>5 Ci for several ‘mini-cycles’	Routine production since about 1986 Backup production for ORNL
BR2	SCK•CEN, Mol, Belgium	~1 Ci, 20+ d cycle; cycle length varies	Experience since about 2001 Backup production for ORNL
ATR	Idaho National Laboratory (INL), Idaho Falls, USA	~0.5 Ci, one cycle expected	Production not yet initiated

To illustrate the importance of ^{188}W backup production capabilities, in 1998 ORNL and SCK•CEN successfully demonstrated that the BR2 reactor in Mol, Belgium, can serve as an important ^{188}W production site [5.39]. The ^{186}W irradiated targets were processed at ORNL, and the processed ^{188}W was provided to MAP Medical in Finland for fabrication of $^{188}\text{W}/^{188}\text{Re}$ generators for distribution to sites throughout the world for IAEA supported radiopharmaceutical development research projects. In addition, during the HFIR refurbishment in 2001, ORNL purchased irradiation services at the BR2 reactor, processed the irradiated targets at ORNL and distributed the $^{188}\text{W}/^{188}\text{Re}$ generators to customers through the ORNL Isotope Business Office. Customers reported that the $^{188}\text{W}/^{188}\text{Re}$ generators manufactured with lower specific activity ^{188}W produced in the BR2 reactor could be used for, for example, patient studies, bone pain palliation, restenosis therapy, liver cancer therapy and arthritis therapy, with acceptable performance.

The new research reactor under construction at the China Institute of Atomic Energy (CIAE) in Beijing (see <http://www.iaea.org/worldatom/rrdb/>) is reported to have a thermal flux greater than 3×10^{15} neutrons \cdot cm $^{-2}$ \cdot sec $^{-1}$ and would thus be expected to represent another important resource for the production of ^{188}W with even higher specific activity than that currently available.

5.5.3. Direct reactor production of ^{188}Re

Although use of $^{188}\text{W}/^{188}\text{Re}$ generators is the most convenient and cost effective method for obtaining no-carrier-added ^{188}Re on a routine basis, an alternative that should be mentioned for providing ^{188}Re in regions where a high flux research reactor is not available is the direct production of ^{188}Re from neutron irradiation of enriched ^{187}Re . With the 16.9 h physical half-life, distribution of ^{188}Re within a city or region is certainly possible, especially when the specific activity is not an issue, such as for the preparation of ^{188}Re labelled HEDP for bone pain palliation/therapy and particles for treatment of rheumatoid arthritis [5.40].

5.6. PROCESSING OF ^{188}W

5.6.1. Tungsten metal and tungsten oxide targets

Although a variety of post-irradiation processing strategies are possible, processing of ^{188}W has usually involved post-irradiation basic dissolution of ^{186}W oxide targets and/or high temperature oxidative processing of metallic enriched

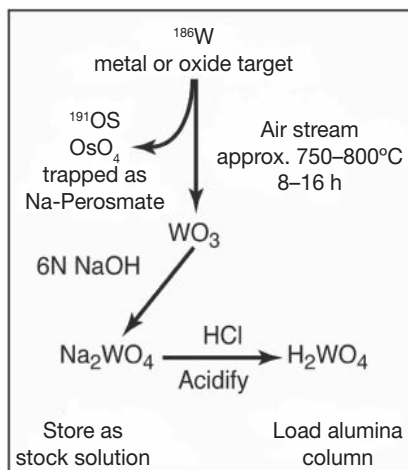


FIG. 5.6. ORNL post-irradiation processing scheme for pressed/sintered enriched ^{186}W metal targets.

^{186}W targets [5.31–5.33]. Relatively large enriched ^{186}W targets are required to produce multicurie levels of ^{188}W . Use of granular/powder oxide targets can simplify the processing, since dissolution in sodium hydroxide solution with heating is straightforward. Powder enriched ^{186}W targets are routinely used for production of ^{188}W at the SM reactor at the Research Institute of Atomic Reactors (RIAR) in Dimitrovgrad, Russian Federation. However, although powder metal or oxide targets were routinely used for ^{188}W production in the ORNL HFIR for many years [5.31–5.33], transition to use of the highly enriched ^{186}W pressed and sintered targeted geometry was originally explored as a strategy to increase the ^{186}W mass per target [5.35]. More recently, the pressed discs have become the target of choice at ORNL because of the requirements for use of available hot cells and the need to minimize hot cell contamination resulting from potential release of the highly radioactive powder. In this case, if it is required, subsequent removal of any radionuclide impurities is possible, such as with ion exchange chromatography as is used at RIAR.

5.6.2. Post-irradiation processing of pressed/sintered enriched ^{186}W at ORNL

If metallic granular/powder or pressed/sintered enriched ^{186}W targets are used, as at ORNL, the irradiated target material is first heated to 750–800°C in a quartz furnace while a stream of air is passed over the target material for conversion to tungsten oxide for subsequent dissolution in base, as shown in Figs 5.6 and 5.7. In this case, the contaminating levels of most of the ^{191}Os

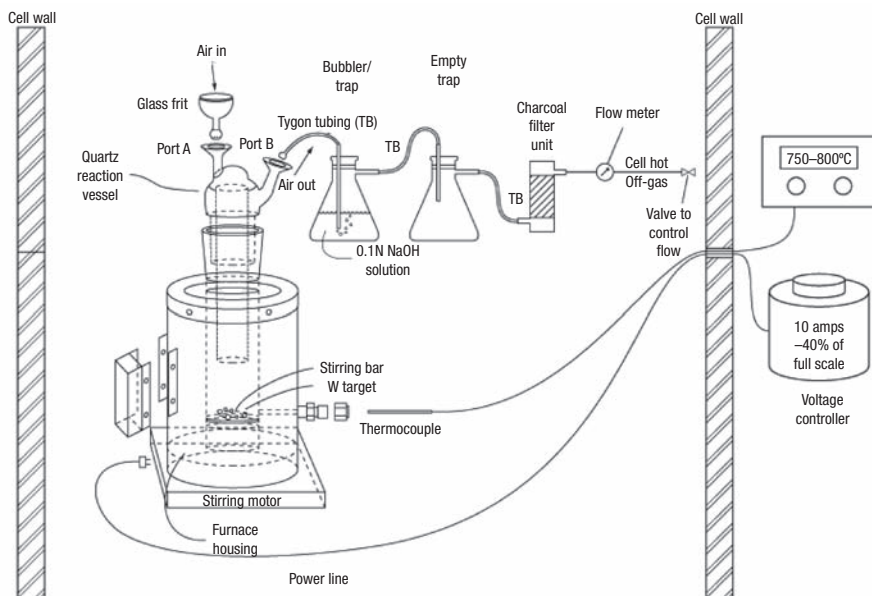


FIG. 5.7. Apparatus used at ORNL for post-irradiation conversion of metallic enriched ^{186}W targets to tungsten oxide.

radionuclidic impurities are also swept away from the target for subsequent trapping in base. At ORNL, the resulting sodium tungstate stock solution is not purified further, since the possible presence of low amounts of the ^{191}Os and ^{192}Ir impurities present in the ^{188}Re generator eluents used for radiopharmaceuticals preparation has been shown to be inconsequential.

5.6.3. Post-irradiation processing of powder enriched ^{186}W oxide targets at RIAR

At RIAR, highly enriched ^{186}W oxide targets are used for the production of ^{188}W ; a schematic view of the apparatus used for powder target processing is given in Fig. 5.8 [5.41, 5.42]. The sealed quartz tube containing the irradiated target material (component No. 3 in Fig. 5.8) is transferred through the funnel unit (component No. 2) into a tube into which a screw (component No. 4) has been inserted, and the cover (component No. 1) is then placed on the unit. The quartz tube is then positioned with the screw (component No. 4) and crushed by insertion of a second screw (component No. 5). The crushed ampoule with the irradiated enriched ^{186}W contents then falls into the dissolver body (component No. 6), and processing of the targets by dissolution in sodium hydroxide solution begins.

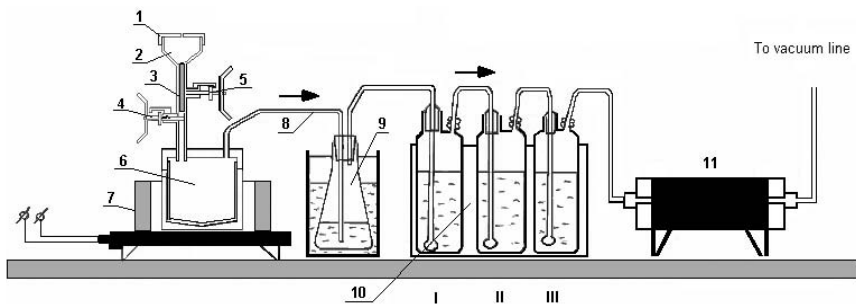


FIG. 5.8. Apparatus used at RIAR for crushing and dissolution of irradiated W targets. Components are as follows: (1) cover with air inlet; (2) funnel; (3) capsules of irradiated ^{186}W ; (4) screw to position capsule; (5) screw to crush capsule; (6) dissolver body; (7) hot plate; (8) vapour exhaust pipe; (9) flask for condensate collection; (10) traps; (11) charcoal traps.

The ^{188}W is produced by neutron irradiation of enriched ^{186}W (enrichment $>96\%$). Tungsten oxide sealed in quartz capsules is used as the target. The capsules are placed in a stainless steel ampoule, sealed by welding and irradiated in the SM reactor. After irradiation and a 9–10 d cooling period, required for decay of ^{187}W ($T_{1/2}$: 23.8 h), the irradiated targets are transferred to the shielded cell K-03, where they are cut mechanically to remove the quartz capsules containing the ^{186}W enriched tungsten oxide; these are transported into the shielded box through a system of conveyors, where they are decontaminated by consecutive washing with nitric acid, water and alcohol. The quartz tubes are then opened mechanically (crushed) using the apparatus shown in Fig. 5.8.

To increase the safety of the reprocessing of irradiated tungsten oxide, a special apparatus was developed whose design essentially reduces the probability of radionuclide ingress (first of all, ^{191}Os) into the box atmosphere and ventilation system (Fig. 5.7). The main element of the apparatus is a tungsten oxide dissolver whose body is fabricated of stainless steel and allows disassembly and assembly in a manipulator type box. The dissolver comprises a screw device for crushing the quartz capsules, a Teflon vessel intended for dissolution, and a piping system for reagent supply, product sampling and air circulation.

Irradiation of tungsten oxide at high thermal neutron flux in a high flux reactor results in formation of a tungsten oxide phase, which is very difficult to dissolve in alkali and acids [5.31, 5.33, 5.42, 5.43]. For this reason, sodium tungstate is obtained by dissolution of tungsten oxide under long continuous heating (3–5 h) in sodium hydroxide solution containing an additive of 5% sodium hypochlorite solution. On completion of the tungsten oxide dissolution, the resulting solution is filtered through a Teflon-wool filter to remove mechanical particles (splinters of quartz glass) and evaporated to a minimum

volume. The solution is then diluted with water and either transferred to certification and packaging or subjected to further purification by ion exchange chromatography. The environmental consequences of the formation of impurities are discussed in Section 5.7.

During dissolution of the tungsten oxide, including such operations as crushing of the quartz capsules, introduction of alkaline solution, dissolution of the oxidizing agent, heating and evaporation (as shown in Fig. 5.8), the dissolver is connected to a vacuum system providing constant circulation of the air. Although it is similar to the system used at ORNL, in the system at RIAR the radioactive gaseous ^{191}Os in the form of OsO_4 is transported into a system of traps containing hydrochloric acid solution of thiourea (trap I) and mixed sodium alkali and ethanol (traps II and III). The traps are able to absorb OsO_4 , resulting in chemical reaction with the trap solutions, which leads to formation of non-volatile Os compounds. The operation efficiency of the traps has been experimentally validated. Nearly all the ^{191}Os is entrapped by the first trap with thiourea. The trap with the alkaline solution performs a double function: it entraps Os, and the alkaline solution neutralizes the hydrochloric acid vapours that arise in the first trap, which prevents corrosion of the stainless steel piping of the vacuum system. Moreover, the trapping system described above is additionally equipped with traps containing activated charcoal, which entraps aerosols and splashes arising in traps I–III and allows for chemical binding of OsO_4 .

5.6.4. Radionuclide impurities

5.6.4.1. HFIR produced ^{188}W at ORNL

As described in Section 5.5.1 and shown in Fig. 5.5, both ^{191}Os and ^{192}Ir are formed during irradiation of ^{186}W targets; the levels produced depend upon the irradiation parameters. However, at secular equilibrium, these two radionuclide impurities usually are not detected in the gamma spectrum of ^{188}W and ^{188}Re (Fig. 5.9) because of the intensity of the 159 keV gamma photon emitted from ^{188}Re . Currently, processing of HFIR produced ^{188}W at ORNL involves heating the irradiated ^{186}W enriched pressed/sintered discs to high temperatures (750–800°C) in a quartz vessel housed in a furnace [5.35] under ambient air flow. The exhaust is then passed through a drain consisting of a basic trap and an activated carbon filter unit (see Figs 5.6 and 5.7). Use of the solid targets greatly minimizes the possibility of in-cell contamination during transfer procedures, which is an important benefit since the heavily shielded hot cells used for this process must be opened for transfer of supplies, etc. The cell exhaust then passes through an in-cell high efficiency particulate air (HEPA) filter unit and

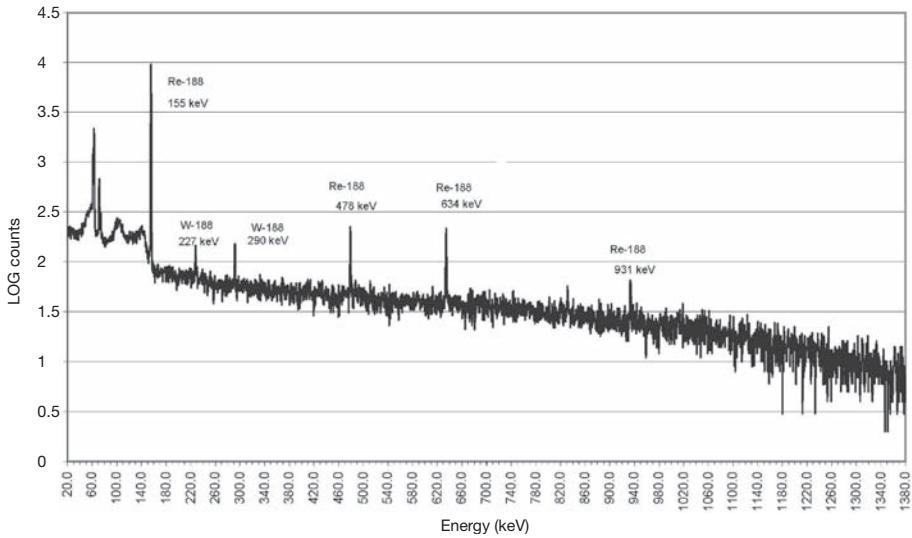


FIG. 5.9. Typical gamma spectrum of ^{188}W produced in the ORNL HFIR (^{188}W target NM-716 solution (log scale), 30 min scan).

subsequently through another large HEPA filter bank, before passing through a monitored stack. With routine use of this system, no release of ^{191}Os through the stack has been detected. The volatile Rh species released from the target during the high temperature process are found coating the cool upper surfaces of the quartz processing vessel (see Fig. 5.7).

The occasional presence of very low levels of ^{60}Co detected by gamma spectroscopy of the decayed ^{188}Re bolus obtained from ORNL-produced $^{188}\text{W}/^{188}\text{Re}$ generators probably results from activation of the low levels of natural cobalt (^{59}Co) present in the Al material used to construct the hydraulic tube units. It is assumed that, after irradiation, small amounts of the Al base material probably accompany the irradiated ^{186}W material, which is removed after opening the hydraulic tube assembly. Encapsulation of the ^{186}W target material in high purity quartz ampoules prior to insertion in the secondary hydraulic tube unit is a strategy that was used in the past to avoid any ^{60}Co impurity in the processed ^{188}W . However, for the enriched ^{186}W target masses, which exceed 1 g, the quartz primary encapsulation unit was always found to be shattered when the Al hydraulic tube unit was opened, thus allowing the W to come into contact with the Al base material. Because target masses of about 5 g are now routinely irradiated, the quartz primary containment in the target tube is no longer used.

Most of the ^{191}Os is removed during the oxidative conversion of the metallic W target to tungsten oxide, and any remaining ^{191}Os and ^{192}Ir is generally only detected in small amounts by gamma spectroscopy following decay of ^{188}Re

TABLE 5.3. ANALYTICAL CHARACTERISTICS OF PROCEDURES FOR DETERMINATION OF IMPURITY CONTENT IN ^{188}W PRODUCED AT RIAR

Element	Spectroscopic carrier	Element yield (%)	Overall measurement uncertainty (%)	Minimum measurable concentration (mg/L)
Al	Ba	81	31.6	0.3
	Tl, Ga	110	31.5	
Cr	Ba	86.0	23.0	0.3
	Tl, Ga	75.0	32.0	
Fe	Ba	88.0	27.0	0.3
	Tl, Ga	77.5	35.0	
Cd	Ba	93.0	21.0	1.0
	Tl, Ga	86.5	29.0	
Ni	Ba	26.0	26.0	0.3
	Tl, Ga	27.0	27.0	
Mg	Ba	34.0	34.0	0.1
	Tl, Ga	30.0	30.0	
Co	Tl, Ga	27.0	27.0	1.0
Zn	Tl, Ga	13.0	13.0	1.0

in the saline eluted bolus. These impurities are slowly eluted from the generators in only very small amounts. If the tandem cation/anion post-concentration system is used, as is the general practice in most clinical centres, essentially all the ^{192}Ir is trapped on the column during concentration.

5.6.4.2. *SM reactor-produced ^{188}W : Chemical concentration and emission spectral determination of impurities in the ^{188}W product*

At RIAR, a convenient method has been developed involving preliminary removal of the bulk of W, followed by impurity determination using emission spectral analysis. Three methods for separation of W and impurity elements were evaluated: anion exchange chromatography, co-precipitation of impurities with a collector and precipitation of tungstic acid. The best results were achieved with tungstic acid precipitation, which is implemented by acidifying the assayed basic solution of sodium tungstate with concentrated nitric acid (Table 5.3). The conditions for separation of chemical impurities from W as well as the composition of the Tl and Ga spectroscopic carriers and spectrum excitation

conditions were optimized. The conditions for separation of impurities from W involve the use of nitric acid at a concentration of 8 mol/L at a temperature of 80°C with a precipitation period (maturing of precipitate) of 15 min. The conditions for spectrographic determination of the elements were as follows: For Cr, Ni, Al, Cu, Co and Fe, the mass of Tl on the electrode was 78.6 and that of Ga was 150 µg, the current was –11 A and the exposure time was 23 s. For Cd, Zn, Mg and Ca, the mass of Tl on the electrode was 456 and that of Ga was 480 µg, the current was –16 A and the exposure time was 23 s.

5.6.5. Purification of ^{188}W from radionuclide impurities

Impurities are produced from W nuclei (^{192}Ir , ^{191}Os ; see Section 5.5.1), as well as from impurities of the target material (^{60}Co , ^{51}Cr , ^{65}Zn , etc.) [5.44, 5.45]. The final product can also be contaminated during processing of the irradiated target material. Nevertheless, there are no particular requirements for the degree of purity of the target material. Owing to the considerable difference in chemical properties of W and the above mentioned elements, the latter are almost fully removed from W during generator washing after fabrication or in the first few cycles of ^{188}Re elution. The activity levels of Ir and Os radioisotopes in the first cycle eluate did not exceed 10^{-6} , according to the work reported in Ref. [5.41], and the levels of other radionuclides were also negligible during generator operation [5.42].

Although decreasing the level of impurities is not required for obtaining ^{188}Re of sufficient radionuclidic purity for clinical applications [5.3–5.5], if doing so is considered necessary, this can be done by using a high purity target material or by applying purification procedures, such as those developed at RIAR, after dissolution of the target. One post-processing purification procedure is based on treating the sodium tungstate solution in a mixture of acetic acid and hydrogen peroxide, with subsequent passage through cation exchange resin [5.43]. To perform this procedure, the sodium tungstate basic solution is evaporated to moist salts, and the residue is dissolved in acetic acid solution containing 3–5 vol.% hydrogen peroxide. The solution is passed through the column filled with the KU-2 cation exchanger (an analogue of Dowex-50). Tungsten forms anionic peroxide complexes that are not retained by the resin, whereas many other metals, unable to produce anionic acetate or peroxide complexes, are retained in cationic form and have distribution ratios higher than 10^2 . The tungsten peroxide complexes are destroyed by heating of the purified solution to 60–80°C, with precipitation of tungstic acid.

An additional approach to processing the irradiated ^{186}W target material after conversion of W to a soluble form has also been developed at RIAR. Normally, ^{188}W is supplied as sodium tungstate solution in sodium hydroxide or as tungsten oxide. Accordingly, two approaches were developed at RIAR to

prepare these products for shipment. Shipment as sodium tungstate involves adjusting the bulk activity of the solution with an appropriate concentration of sodium hydroxide, followed by packing of the product. This approach may require minimization of the excess of sodium hydroxide used to dissolve the irradiated material when subsequent purification is not undertaken. The product contains all the products used at the dissolution stage as well as impurities generated under neutron irradiation.

Another approach is to prepare tungsten oxide and avoid the remote handling of WO_3 powder. The following technique has been developed:

- (1) The solution of sodium tungstate in sodium hydroxide is acidified by nitric acid, leading to precipitation of H_2WO_4 .
- (2) Freshly precipitated tungstic acid is separated from the mother liquor by filtration and dissolved in 6–8 mol/L NH_4OH directly in a filter (readily soluble ammonia tungstate is produced).
- (3) After measuring the bulk activity, an aliquot of the solution is transferred into the quartz capsule (which is used as the primary package) and evaporated to dryness.
- (4) The dry residue is sintered at 600–650°C to decompose ammonia tungstate to tungsten oxide.

It should be noted that nitric acid should be used for this process, as hydrochloric acid is not suitable, since W forms soluble chloride complexes. Moreover, a depolarization agent such as gelatine should also be added to ease sedimentation of tungsten acid. The gelatine is added in a very small quantity (a few drops of 0.2–0.3% water solution) and is destroyed following the generation of tungsten oxide. Precipitation of tungstic acid and its separation from the mother liquor allows a convenient method for purification of ^{188}W from alkali, alkali earth, rare earth and some transition metal impurities with factors higher than 10^2 .

Based on an analysis of the last two data referenced in Table 5.4 for targets obtained during production of ^{188}W , it can be concluded that the most important parameter of the irradiation mode is the duration of the last irradiation ‘microcycle’, owing to features of production and decay kinetics of short lived ^{187}W . The ^{188}W specific activity can differ considerably (e.g. 6.3 versus 10.1 Ci/g) when there are even minor differences between campaign durations and the last microcycle duration (23.6 and 25.5 effective days), and considerable differences can arise if the duration of the last microcycle is short (6 and 9 effective days).

TABLE 5.4. PARAMETERS FOR ROUTINE PROCESSING OF IRRADIATED ^{186}W AT RIAR

Target weight (mg)	Irradiation time (duration of microcycles, eff. days)	^{186}W burnup (%)	^{188}W yield (Ci/g ^{186}W at EOI)
758.8	19.7	24.4	3.95
1911.7	17.5	17.5	4.7
2970.0	19.9	22.9	4.68
3132.4	17.7	24.2	4.4
2061.9	23.6 (9+8.6+6)	22.2	4.9
3579.4	25.5 (8+8.5+9)	34.1	6.6

5.7. RADIOLOGICAL CONTROLS AND RADIATION PROTECTION

Although radiological protection and minimization of environmental contamination are prime concerns for the processing of any radioisotope, they are particularly important for the processing of ^{188}W . Highly volatile ^{191}Os species are formed during this production process; as described earlier, special precautions and trapping and monitoring systems must be engineered to ensure that any environmental contamination is within the acceptable regulatory limits.

In addition to the importance of having the appropriate radiological controls and equipment available at the processing facility to avoid the possibility of facility contamination and release of radiocontaminants into the environment, it is also essential to ensure that the processing facility has adequate shielding and contamination control to protect the operating staff. This section describes the issues associated with trapping of radiocontaminants that may be released into the environment and radiation protection of staff, which are important practical factors in the development, installation and utilization of technology for the processing of ^{188}W targets.

5.7.1. Technical controls and radiological assessment at RIAR

5.7.1.1. Analysis and experimental evaluation of the radiation and environmental safety of ^{188}W preparation

In view of enhanced safety requirements for nuclear technologies, the study of radiation and environmental aspects is becoming crucial, along with the development and improvement of technological processes for production of radiochemicals and ionizing sources. The work described here was aimed at

accumulating data that could be used for calculation, experimental validation and certification of technological processes and facility safety. Other goals included the evaluation of possible emission levels of radioactive substances and development of technical and sanitary measures to ensure observance of basic radiation safety regulations and standards. Within the framework of development of ^{188}W processing technology, the goal was to study radiological issues in the workplace during the processing of irradiated W targets. Radiological control involved the following parameters: dose rates within the workplace, contamination levels of the process and shielded equipment, composition and activity of air emissions, and quantity and composition of radioactive waste. The distinctive feature of the studies performed consisted in obtaining all the data during actual production of experimental batches of preparation, rather than during simulation experiments. The activity of the batches corresponded to the planned throughput of the facility under development, thus providing adequate sensitivity of measurement procedures and allowing proper accounting of peculiarities of the radionuclide chemical state in the irradiated material. In addition, some design modifications to the process equipment were introduced, based on analysis of the nature of the radioactive emissions that occurred during the work. These modifications were aimed at minimizing the levels of radioactive emissions and hence ensuring optimal environmental safety during ^{188}W processing.

During neutron irradiation of ^{186}W , ^{188}W formation is accompanied by production of a large group of Re, Os and Ir isotopes (see Fig. 5.5). When analysing the potential environmental hazards of the ^{188}W production process, one goal of these studies was to estimate the activity levels of the radionuclides produced. The activity of ^{191}Os was determined, and special measures were taken to trap its volatile compounds. Consequently, the activity of the irradiated targets at the time of processing is from $^{187,188}\text{W}$, ^{188}Re and ^{191}Os radionuclides. Therefore, the radiation and environmental safety analysis of the ^{188}W production technology focused on the behaviour of these radionuclide species. The radiation–environmental characteristics of the reprocessing of irradiated targets were studied during production of experimental batches of the ^{188}W preparation during 1998–2002. Table 5.5 presents characteristics of the irradiated targets whose processing was carried out with analysis and monitoring of the radiation situation.

The levels of radioactive contamination of the equipment and box surfaces were analysed by taking smears with a dry cotton wad over a 20 cm^2 area. The smears were placed in individual packs and the radionuclide composition was determined by gamma spectrometry. The dose rates of gamma radiation (photon and bremsstrahlung) were measured with a DRGZ-02 dosimeter. The

TABLE 5.5. RADIONUCLIDES PRODUCED IN THE NEUTRON IRRADIATION OF ^{186}W

Radionuclide	Half-life	Estimated radionuclide activity at the end of irradiation at RIAR ((Bq/g)[(Ci/g)] of initial nuclide)
^{187}W	23.8 h	$(1.48-2.59) \times 10^{14} [(4-7) \times 10^3]$
^{188}W	69 d	$(1.48-1.85) \times 10^{11} [4-5]$
^{189}W	11 min	— ^a
^{188}Re	17 h	$(1.48-1.85) \times 10^{11} [4-5]$
^{189}Re	23.4 h	— ^b
^{191}Os	15.4 d	$(1.85-3.7) \times 10^9 [0.05-0.1]$
^{192}Ir	74 d	$(1.11-1.85) \times 10^8 [0.003-0.005]$

^a No reliable data for calculation; activity was not measured because of the short half-life.

^b Yield was insignificant.

measurement uncertainty was 25% in the 20–1500 keV energy range (according to the metrological certification data of the instrument).

5.7.1.2. Efficiency of radionuclide trapping by analytical filters at RIAR

For work carried out on stationary equipment (i.e. a cell or box) having an adequate thickness of shielding, the radiation dose does not exceed the dose limit and can be considered to be allowable. Tungsten and Re do not form any volatile compounds when subjected to these processing conditions, and thus can only pass into the box atmosphere in the form of quickly settling large drops (splashes) arising during evaporation of the solution, or in the form of aerosols that are readily trapped by the filters of the ventilation system. In the processing of the irradiated ^{186}W targets, the main hazard is possible ingress of volatile forms of ^{191}Os such as $^{191}\text{OsO}_4$ into the box or shielded cell atmosphere, which can then pass into the ventilation system. Therefore, the amount of air (aerosol) emission of radioactive substances was chosen as a basic criterion in the environmental safety analysis of the ^{188}W preparation production process.

The first pair of filters in the set trapped 80% of the ^{191}Os and 100% of the ^{188}W and ^{188}Re . The ratio of trapped radionuclides was estimated relative to the total activity of each radionuclide measured on the filter. The validity of this evaluation as well as the conclusion regarding sufficient efficiency of the involved filter sets are supported by the fact that ^{188}Re and ^{188}W were detected only on the first filter in the set. The ^{191}Os radionuclide was found on all four filters, but more than 80% of its activity was measured on the first filter, with

15% on the second, 3% on the third and less than 1% on the fourth filter. The decontamination factor from ^{191}Os achieved 6–7 on each filter; the total trapping efficiency exceeded 98%.

5.7.1.3. Emissions of radioactive substances

In the processing of irradiated W targets, operations such as crushing the quartz capsules, dissolving the tungsten oxide and evaporating the resulting solution are potentially the most hazardous (according to the chosen ‘amount of air (aerosol) emission’ criterion). When the capsules are opened (mechanically crushed; see Fig. 5.8), the possibility exists for the formation of tungsten oxide aerosol particles (dusting), which can cause radioactive contamination of the process and shielded equipment. However, ingress of aerosol particles into the ventilation system is unlikely because of their large size and the high efficiency of the filtering elements installed at the connections of air ducts.

At the same stage there is a possibility of release of radioactive products in gaseous form, in particular, osmium tetroxide. The dissolution of tungsten oxide and evaporation of the resultant solution are carried out at high temperatures; therefore, these processes can be accompanied by splashing of the solution and formation of aerosols, as well as by release of gaseous volatile products. The ingress of W and Re into the ventilation system was considered unlikely, since there were no appropriate conditions in the applied technological process for formation of their gaseous products. Therefore, no special measures were taken to prevent release of ^{191}Os into the box atmosphere. In particular, the quartz capsules were crushed directly in the uncovered beaker intended for dissolution. The gaseous and vaporous products, including aerosols, released at the dissolution stage were entrapped by a standard ‘umbrella’ type trap, which was mounted over the beaker and connected to the exhaust vacuum system (see Fig. 5.8). The design of the dissolver did not exclude ingress of vapours and volatile compounds into the box atmosphere, and then into the ventilation system, at the moment when additional portions of reagents were introduced into the dissolution beaker.

The major part of the ^{191}Os activity ($\sim 10^8$ Bq/d) was recorded in the air of the ventilation system (collector No. 4) during mechanical crushing of the quartz capsule. The ^{188}Re and ^{188}W activity levels detected in the emissions were lower by three orders of magnitude ($\sim 10^5$ Bq/d) and did not exceed the 2% control level established for the special building ventilation system. At the stage of tungsten oxide dissolution in alkali without any oxidizing agent and with interim evaporation of the solution, the amount of ^{191}Os emission was $(2-5) \times 10^5$ Bq/d, which was less than 1% of the emission produced in the first operation. The activity of ^{188}Re and ^{188}W in the emission was reduced by a factor of 2–5.

The dissolution of the irradiated material in alkali did not transfer W to a soluble form completely; therefore, an oxidizing agent (sodium hypochlorite) was added to the solution after three dissolution cycles in alkali (see Ref. [5.4]). Under these conditions, the oxidation rate of Os and Re changes, resulting in the formation of volatile OsO_4 and Re_2O_7 . Decomposition of the oxidizing agent is accompanied by the formation of gaseous products (Cl, in particular), which stimulates aerosol formation. This contributed to the amount of emissions measured in the ventilation system collector (operation III). Subsequent operations (namely, filtration of the solution and its evaporation) were also accompanied by transition of radionuclides into the gaseous phase, with the major part of activity being determined by ^{191}Os . The reason for this is the gradual decomposition of the oxidizing agent during evaporation.

The most intensive Os transition into the gaseous phase was observed during evaporation of the solution to dry salts, because the temperature of the residual salt in this process increases significantly and exceeds the boiling point of osmium tetroxide (120°C). The Re and W emissions at these stages are probably caused by aerosol formation during boiling of the solution. It should be noted that the ratio of the ^{188}Re and ^{188}W activity levels measured in the emission do not correspond to the equilibrium ratio of this generator pair and cannot be explained by assumption of a mechanical origin of the tungsten oxide aerosol particles at the stage of quartz capsule crushing. The nature of this divergence is unclear, indicating that additional studies are necessary involving a special methodology. The analysis of the results obtained in the reprocessing of one of the targets (No. 84) indicated that the most probable reason for radionuclide presence in the air emissions was the low efficiency of the aerosol and vapour trapping system, that is, the 'umbrella' type trap placed over the beaker where all operations were carried out. In the next reprocessing (target No. 92), the design of the trap was modified and the umbrella shaped part was placed inside the dissolution beaker, with minimal clearances left between the umbrella and the beaker. According to the results of the reprocessing, this modification allowed a significant decrease in the activity of the air emissions. While a larger amount (activity) of the material was processed, the overall emission of ^{191}Os was lower (84 MBq) and the principal quantity of Os passed into the gaseous phase at the stage of dissolution in the presence of the oxidizing agent.

It should be noted that at this stage an emission of ^{188}Re was also detected that confirmed the formation of volatile rhenium oxide similar to that described elsewhere [5.35]. However, the ^{188}Re activity in the emission was about one hundred times less than that of ^{191}Os . A part of the Re had passed into the gaseous phase at the stage of solution evaporation during its packaging, evidently due to incomplete decomposition of the oxidizing agent.

The trapping system developed for use at RIAR not only enhanced the environmental safety of the technological process but also allowed experimental estimation of the ^{191}Os yield during irradiation of ^{186}W in the SM reactor (Table 5.6). The average ^{191}Os yield was 2.6–2.9 GBq/g of ^{186}W ; however, depending on the irradiation parameters, this value varied significantly for some targets. These data can be useful in analysis of the nuclear constants system characterizing the formation of radionuclides during irradiation of ^{186}W . The reliability of the proposed equipment flowsheet was demonstrated by the processing of several irradiated ^{186}W tungsten targets during the 2000–2001 period.

During the 2001–2003 period, no emission of radioactive ^{191}Os into the RIAR ventilation system was recorded at the stage of tungsten oxide dissolution. However, the control level of daily emissions into the ventilation system was exceeded in the reprocessing of targets 84 and 88 at the stage of evaporation of sodium tungstate prior to packaging for shipment. The reason for the emission was incomplete distillation of ^{191}Os at the stage of tungsten oxide dissolution, probably due to a deficiency of the oxidizing agent. In view of this fact, some design modifications were introduced to the sodium tungstate solution evaporator. In particular, the system for local removal of resulting vapour was connected to the Os trapping system used at the stage of dissolution. This reduced

TABLE 5.6. EXPERIMENTAL ESTIMATION OF THE ^{191}Os YIELD IN SM REACTOR PRODUCTION OF ^{188}W

(based on the results of reprocessing campaigns carried out during the 2001–2002 period)

No.	Target ID	^{188}W activity at the time of reprocessing (GBq)	^{191}Os activity in traps (at the moment of activity measurement, MBq)			^{191}Os yield on completion of irradiation (GBq/g of ^{186}W)
			Trap No. 1	Trap No. 2	Trap No. 3	
1	55	73.6	353	9.62	0.004	2.59
2	67	62.7	414	0.89	0.007	2.78
3	84	87.3	455	0.85	0.002	2.74
4	88	24.4	297	32.6	0.222	6.36
5	13	67.3	659	24.5	0.011	2.89
6	75	136.0	114	192	0.022	2.85
7	24	188.0	898	0.29	0.003	1.22

the probability of contamination of the box atmosphere with ^{191}Os . In addition, quality requirements for the reagents involved in the reprocessing were introduced as an administrative measure to decrease the emission probability. In particular, the oxidizing agent should be prepared immediately prior to dissolution of the targets. The totality of the measures taken should provide a sufficient level of environmental safety for the developed technological process.

5.7.1.4. Surface radioactive contamination of process and shielded equipment

The measurements of activity and radionuclide composition were taken at different points on horizontal and vertical surfaces of the box and equipment used at RIAR for the post-irradiation processing of ^{186}W targets. The smears were taken upon completion of the reprocessing of target No. 84. The data presented indicate that the main contribution to the radioactive contamination is from ^{188}W , ^{188}Re and ^{191}Os .

The activity of ^{187}W at the beginning of the processing is comparable with the activity of ^{188}W and ^{188}Re ; however, by the end of the processing, the ^{187}W activity decreases considerably (for ^{187}W , $T_{1/2}$: 24 h). Therefore, the ^{187}W radionuclide was not detected in the smears taken. It should be noted that the above level of surface contamination was measured at the first stage of the work, when simplified equipment was used; in particular, the dissolution of tungsten oxide and evaporation of the resulting solution was carried out in the uncovered beaker, which did not prevent large splashes of the solution falling onto adjacent surfaces. The modification of the dissolver at the second stage of work practically excludes such a possibility, because all the operations are carried out in a closed system. The experience gained in the processing of irradiated targets at RIAR has demonstrated that surface radioactive contamination of the box and equipment is readily removed by washing with standard washing solutions. The activity of ^{188}W and ^{188}Re contributing to the level of surface contamination did not exceed 10^9 Bq, even when the ‘uncovered’ dissolver was used. The volume of washing solutions used in the box in a standard ‘wash-out’ cleaning cycle is less than 100 L. Consequently, the activity concentration of radioactive substances in the solution supplied to the special liquid waste disposal system does not exceed 10^7 Bq/L, which corresponds to the medium low waste level.

5.7.1.5. Estimation of the radiation environmental impact of ^{188}W processing at RIAR

As determined from the detailed studies conducted at the RIAR facility, emission of radioactive aerosols in the processing of irradiated targets with ^{188}W was mainly from ^{191}Os . The maximum experimentally measured value of ^{191}Os

emission was 3×10^7 Bq, which is close to the control level of 3.7×10^7 Bq/d (by the sum of beta and alpha emitters) established for the production facility (Building 120). The probability of simultaneous failure of all safety barriers (capsule crushing device, dissolver, trapping system, etc.) is extremely low and does not exceed 10^{-6} per year. Even in the case of an accident — for example, in the case of fire — the maximum possible emission of ^{191}Os would be no higher than 1.3×10^9 Bq, which is several orders of magnitude less than the maximum permissible emission established for RIAR.

The data above represent the first accurate experimental measurement of ^{191}Os yield during irradiation of ^{186}W in the high flux SM reactor and can be used for enhancement of the constants in the ^{188}W accumulation chain. A modified design has been developed for the processing equipment used at the stages of quartz capsule crushing and irradiated material dissolution. The equipment design includes safety barriers that significantly reduce the probability of radionuclide release into the box atmosphere and ventilation system. Radioactive waste arising from the technological process of ^{188}W production was estimated. The levels of radioactive waste do not exceed 8% of the activity of the ^{188}W produced. The results of the study can be used in the development of a routine technology for ^{188}W production.

The radiation situation has been studied at the main process stages of ^{188}W production. It has been demonstrated for the first time that the highest contribution to the air activity emission is made by the ^{191}Os radionuclide, whose release in the form of OsO_4 is observed at the stages of crushing the quartz capsules containing irradiated tungsten oxide and dissolution of the tungsten oxide in alkaline solution in the presence of the oxidizing agent. The efficiency of OsO_4 trapping by analytical filters with an SFL-2I-50 carbon band is close to 100%. These filters can be used in combination with AFA-RSP-20 analytical filters to monitor air contamination during production of the ^{188}W preparation.

5.8. CONCLUSION

There continues to be widespread interest in the availability of $^{188}\text{W}/^{188}\text{Re}$ generators and the use of high specific activity ^{188}Re for a variety of important therapeutic applications in nuclear medicine and oncology. The attractive radionuclidic and chemical properties of ^{188}Re and the possibility of obtaining ^{188}Re in-house and on demand make this generator system ideal for many therapeutic applications. Because of the long irradiation periods required to produce ^{188}W in a research reactor and the other costs of generator fabrication and testing, $^{188}\text{W}/^{188}\text{Re}$ generators would not be expected to be inexpensive, and are thus designed for optimal use with maximum utilization of the eluted ^{188}Re

activity. Cost effective use of this generator requires multiple uses of the ^{188}Re , preferably relatively high patient throughput and, ideally, installation in a central radiopharmacy where unit doses can be provided to regional institutions. In this manner, it would be expected that the use of the $^{188}\text{W}/^{188}\text{Re}$ generator for therapeutic applications could become as important as the availability of $^{99\text{m}}\text{Tc}$ from the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator system is for routine diagnostic applications.

ACKNOWLEDGEMENTS

ORNL is managed by UT-Battelle, LLC, for the U.S. Department of Energy, under contract No. DE-AC05-00OR22725. This work was supported by funding from the DOE ER Office of Biological and Environmental Research and the NE Office of Isotopes for Science and Medicine.

REFERENCES TO CHAPTER 5

- [5.1] LAMBERT, B., DE KLERK, J.M.H., Clinical applications of ^{188}Re -labelled radiopharmaceuticals for radionuclide therapy, *Nucl. Med. Commun.* **27** (2006) 223–230.
- [5.2] JEONG, J.M., KNAPP, F.F., Jr., Use of the Oak Ridge National Laboratory tungsten-188/rhenium-188 generator for preparation of the rhenium-188 HDD/lipiodol complex for trans-arterial liver cancer therapy, *Semin. Nucl. Med.* **38** 2 (2008) S19–29.
- [5.3] JEONG, J.M., CHUNG, J.-K., Update: Therapy with ^{188}Re -labeled radiopharmaceuticals: An overview of promising results from initial clinical studies, *Can. Biother. Radiopharm.* **18** (2003) 707–718.
- [5.4] CALLAHAN, A.P., RICE, D.E., KNAPP, F.F., Jr., Re-188 for therapeutic applications from an alumina based W-188/Re-188 radionuclide generator system, *NucCompact* **20** (1989) 3–6.
- [5.5] KNAPP, F.F., Jr., TURNER, J.H., PADHY, A.K., Issues associated with the use of the tungsten-188/rhenium-188 generator and concentrator system and preparation of Re-188 HDD: A report, *World J. Nucl. Med.* **3** (2004) 137–143.
- [5.6] KNAPP, F.F., Jr., Rhenium-188: A generator-derived radioisotope for cancer therapy, *Cancer Biotherapy Radiopharm.* **13** (1989) 337–349.
- [5.7] KNAPP, F.F., Jr., et al., Development of the alumina-based tungsten-188/rhenium-188 generator and use of rhenium-188-labeled radiopharmaceuticals for cancer treatment, *Anticancer Res.* **17** (1997) 1783–1796.
- [5.8] LIEPE, K., KROPP, J., RUNGE, R., KOTZERKE, J., Therapeutic efficacy of rhenium-188-HEDP in human prostate cancer skeletal metastases, *Brit. J. Cancer* **89** (2003) 625–629.

- [5.9] PALMEDO, H., et al., Repeated bone targeted therapy for hormone-refractory prostate carcinoma: Randomized Phase II trial with the new, high-energy radiopharmaceutical rhenium-188-HEDP, *J. Clin. Oncol.* **21** (2003) 2869–2875.
- [5.10] SAVIO, E., et al., Rhenium-188 HEDP: Pharmacokinetic characterization in osseous metastatic patients and clinical evaluation, *BMC Nucl. Med.* **1** (2001) 2.
- [5.11] WOEHRLE, J., et al., Patients with in-stent restenosis: Comparison of intracoronary beta-brachytherapy using a rhenium-188 filled balloon catheter with the polymer-based paclitaxel-eluting taxus-express stent, *Nukelamedizin* **46** (2007) 189–191.
- [5.12] LEE, S.W., et al., Incidence and predictors of late recurrence after beta-irradiation therapy with Re-188-MAG3-filled balloon for diffuse in-stent restenosis, *Am. Heart J.* **151** (2006) 158–163.
- [5.13] REYNEN, K., et al., Intracoronary radiotherapy with a rhenium-188 liquid-filled angioplasty balloon system in in-stent restenosis: A single center, prospective, randomized, placebo-controlled, double-blind evaluation, *Coronary Artery Disease* **17** (2006) 371–377.
- [5.14] SHIN, J.H., et al., Rhenium-188 mercaptoacetyltriglycine-filled balloon dilation in the treatment of recurrent urethral strictures: Initial experience with five patients, *J. Vasc. Intervent. Radiol.* **17** (2006) 1471–1477.
- [5.15] WOHRLE, J., KRAUSE, B.J., NUSSER, T., KOCHS, M., HOHER, M., Repeat intracoronary beta-brachytherapy using a rhenium-188-filled balloon catheter for recurrent restenosis in patients who failed intracoronary radiation therapy, *Cardiovasc. Revasc. Med.* **7** (2006) 2–6.
- [5.16] LEE, S.W., et al., Comparison of angiographic and clinical outcomes between rotational atherectomy versus balloon angioplasty followed by radiation therapy with a rhenium-188-mercaptoacetyltriglycine-filled balloon in the treatment of diffuse in-stent restenosis, *Int. J. Cardiol.* **102** (2005) 179–185.
- [5.17] ZENZ, T., et al., Targeted marrow irradiation with radioactivity labeled anti-CD66 monoclonal antibody prior to allogenic stem cell transplantation for patients with leukemia: Results of a Phase I-II study, *Haematologica* **91** (2006) 285–286.
- [5.18] BUCHMANN, I., et al., Myeloablative radioimmunotherapy with Re-188-*anti*-CD66-antibody for conditioning of high-risk leukemia patients prior to stem cell transplantation: Biodistribution, biokinetics and immediate toxicities, *Cancer Biother. Radiopharm.* **17** (2002) 151–164.
- [5.19] BUCHMANN, I., SCHULTZ, A., SPARBER, M., RESKE, S.N., Myeloablative radioimmunotherapy with ¹⁸⁸Re-ANTI CD-36-mAB in pediatric leukemia patients: A Phase I trial, *J. Nucl. Med.* **43** (2002) 37P.
- [5.20] BUGAJ, J.E., et al., Radiotherapeutic efficacy of a SSTR-targeting peptide (¹⁸⁸Re-P2045) in a small cell lung cancer (SCLC) mouse model, *J. Nucl. Med.* **43** (2002) 123P.
- [5.21] LAMBERT, B., et al., ¹⁸⁸Re-HDD/Lipiodol therapy for hepatocellular carcinoma: A Phase I clinical trial, *J. Nucl. Med.* **46** (2005) 60–66.
- [5.22] BERNAL, P., et al., International Atomic Energy Agency-sponsored multinational study of intra-arterial rhenium-188-labeled Lipiodol in the treatment of inoperable hepatocellular carcinoma: Results with special emphasis on prognostic value of dosimetric study, *Semin. Nucl. Med.* **38** 2 (2008) S40–S45.

- [5.23] KUMAR, A., et al., Inoperable hepatocellular carcinoma: Transarterial ^{188}Re HDD-iodized oil for treatment – Prospective multicentre clinical trial, *Radiology* **243** (2007) 509–519.
- [5.24] PADHY, A.J., et al., Rhenium-188 Lipiodol therapy of hepatocellular carcinoma: Results of a multicentre-multinational study, *World J. Nucl. Med.* **6** (2007) S55–S557.
- [5.25] KUMAR, A., et al., Management of multiple intrahepatic recurrences after radiofrequency ablation of hepatocellular carcinoma with rhenium-188-HDD-Lipiodol, *Eur. J. Gastroenterol. Hepatol.* **18** (2006) 219–223.
- [5.26] KUMAR, A., SRIVASTAVA, D.N., BAL, C., Management of postsurgical recurrence of hepatocellular carcinoma with rhenium-188-HDD labeled iodized oil, *J. Vasc. Interv. Radiol.* **17** (2006) 157–161.
- [5.27] LAMBERT, B., et al., ^{188}Re -HDD/Lipiodol therapy for hepatocellular carcinoma: An activity escalation study, *Eur. J. Nucl. Med.* **33** (2006) 344–352.
- [5.28] PADHY, A.K., DONDI, M.A., Report on the implementation aspects of the International Atomic Energy Agency’s first doctoral coordinated research project: Management of liver cancer using radionuclide methods with special emphasis on trans-arterial radio-conjugate therapy and internal dosimetry, *Semin. Nucl. Med.* **38** 2 (2008) S5–S12.
- [5.29] LIEPE, K., et al., Feasibility of high activity rhenium-188-microsphere in hepatic radioembolization, *Jpn. J. Clin. Oncol.* **37** (2007) 942–950.
- [5.30] BOSCHI, A., et al., A kit formulation of the preparation of Re-188-Lipiodol: Preclinical studies and preliminary therapeutic evaluation in patients with unresectable hepatocellular carcinoma, *Nucl. Med. Commun.* **25** (2004) 691–699.
- [5.31] CALLAHAN, A.P., MIRZADEH, S., KNAPP, F.F., Jr., Large-scale production of tungsten-188, *Radioact. Radiochem.* **3** (1992) 46–48.
- [5.32] MIRZADEH, S., KNAPP, F.F., Jr., CALLAHAN, A.P., “Production of tungsten-188 and osmium-194 in a nuclear reactor for new clinical generators”, in *Proc. Int. Conf. on Nuclear Data for Science and Technology* (QAIM, S.M., Ed.), Jülich, 1991, 595.
- [5.33] KNAPP, F.F., Jr., CALLAHAN, A.P., BEETS, A.L., MIRZADEH, S., HSIEH, B.-T., Processing of reactor-produced tungsten-188 for fabrication of clinical scale alumina-based tungsten-188/rhenium-188 generators, *Appl. Rad. Isot.* **45** (1994) 1123–1128.
- [5.34] GARLAND, M., Neutronic Effects of Tungsten-186 Double Neutron Capture, PhD Thesis, Univ. Maryland (2004).
- [5.35] MIRZADEH, S., DU, M., BEETS, A.L., KNAPP, F.F., Jr., Thermoseparation of neutron-irradiated tungsten from Re and Os, *Indust. Engineering Chem. Res.* **39** (2000) 3169–3172.
- [5.36] MIRZADEH, S., KNAPP, F.F., Jr., LAMBRECHT, R.M., Burn-up cross section of ^{188}W , *Radiochim. Acta* **77** (1997) 99–102.
- [5.37] KNAPP, F.F., Jr., MIRZADEH, S., BEETS, A.L., tungsten-188/rhenium-188 generators using tungsten-188 reactor-produced from irradiation of natural tungsten targets, *J. Nucl. Med.* **41** (Suppl.) (2000) 149P.
- [5.38] MUSHTAQ, A., Recovery of enriched ^{186}W from spent $^{188}\text{W}/^{188}\text{Re}$ generators, *Appl. Radiat. Isot.* **47** (1996) 727–729.
- [5.39] PONSARD, B., et al., The tungsten-188/rhenium-188 generator: Effective coordination of tungsten-188 production between the HFIR and BR2 reactors, *J. Radioanal. Nucl. Chem.* **257** (2003) 169–174.

- [5.40] SAVIO, E., et al., ^{188}Re radiopharmaceuticals for radiosynovectomy: Evaluation and comparison of tin colloid, hydroxyapatite and tin-ferric hydroxide macroaggregates, *BioMed Central* **4** 1 (2004) 1.
- [5.41] TOPOROV, Y.G., TARASOV, Y.G., KUZNETSOV, R.A., GONTCHAROVA, G.V., “Production of W-188”, Book of Abstracts, Second Russian Conf. on Radiochemistry, Dimitrovgrad, 1997, RIAR, Dimitrovgrad (1997) 265 (in Russian).
- [5.42] KUZNETSOV, R.A., Purification of W-188 from impurities — Technology for ^{188}W - ^{188}Re generator: Current status and development prospects (review), RIAR, Dimitrovgrad, 2003 (in Russian).
- [5.43] INTERNATIONAL ATOMIC ENERGY AGENCY, Manual for Reactor Produced Radioisotopes, IAEA-TECDOC-1340, IAEA, Vienna (2003).
- [5.44] KIRILLOVICH, A.P., et al., Analysis and experimental evaluation of radiation and environmental safety of the tungsten-188 preparation production, *Proc. Res. Inst. At. React. Dimitrovgrad* **4** (2004) 67–80 (in Russian).
- [5.45] KODINA, G., TULSKAYA, T., GUREEV, E., “Production and investigation of rhenium-188 generator”, *Technetium and Rhenium in Chemistry and Nuclear Medicine*, Vol. 3, Raven Press, New York (1990) 635.

CONTRIBUTORS TO DRAFTING AND REVIEW

Filosofov, D.V.	Joint Institute for Nuclear Research, Russian Federation
Garland, M.	Oak Ridge National Laboratory, United States of America
John, K.D.	Los Alamos National Laboratory, United States of America
Knapp, F.F., Jr.	Oak Ridge National Laboratory, United States of America
Kuznetsov, R.	Research Institute of Atomic Reactors, Russian Federation
Mausner, L.	Brookhaven National Laboratory, United States of America
Mirzadeh, S.	Oak Ridge National Laboratory, United States of America
Pillai, M.R.A.	International Atomic Energy Agency
Ponsard, B.	SCK•CEN, Belgium
Roesch, F.	Institute of Nuclear Chemistry, University of Mainz, Germany
Ruth, T.J.	TRIUMF, Canada
Samanta, S.K.	Bhabha Atomic Research Centre, India

Consultants Meeting

Vienna, Austria: 18–22 August 2008



IAEA

International Atomic Energy Agency

No. 22

Where to order IAEA publications

In the following countries IAEA publications may be purchased from the sources listed below, or from major local booksellers. Payment may be made in local currency or with UNESCO coupons.

AUSTRALIA

DA Information Services, 648 Whitehorse Road, MITCHAM 3132
Telephone: +61 3 9210 7777 • Fax: +61 3 9210 7788
Email: service@dadirect.com.au • Web site: <http://www.dadirect.com.au>

BELGIUM

Jean de Lannoy, avenue du Roi 202, B-1190 Brussels
Telephone: +32 2 538 43 08 • Fax: +32 2 538 08 41
Email: jean.de.lannoy@infoboard.be • Web site: <http://www.jean-de-lannoy.be>

CANADA

Bernan Associates, 4501 Forbes Blvd, Suite 200, Lanham, MD 20706-4346, USA
Telephone: 1-800-865-3457 • Fax: 1-800-865-3450
Email: customer-care@bernan.com • Web site: <http://www.bernan.com>

Renouf Publishing Company Ltd., 1-5369 Canotek Rd., Ottawa, Ontario, K1J 9J3
Telephone: +613 745 2665 • Fax: +613 745 7660
Email: order.dept@renoufbooks.com • Web site: <http://www.renoufbooks.com>

CHINA

IAEA Publications in Chinese: China Nuclear Energy Industry Corporation, Translation Section, P.O. Box 2103, Beijing

CZECH REPUBLIC

Suweco CZ, S.R.O., Klecakova 347, 180 21 Praha 9
Telephone: +420 26603 5364 • Fax: +420 28482 1646
Email: nakup@suweco.cz • Web site: <http://www.suweco.cz>

FINLAND

Akateeminen Kirjakauppa, PO BOX 128 (Keskuskatu 1), FIN-00101 Helsinki
Telephone: +358 9 121 41 • Fax: +358 9 121 4450
Email: akatilaus@akateeminen.com • Web site: <http://www.akateeminen.com>

FRANCE

Form-Edit, 5, rue Janssen, P.O. Box 25, F-75921 Paris Cedex 19
Telephone: +33 1 42 01 49 49 • Fax: +33 1 42 01 90 90
Email: formedit@formedit.fr • Web site: <http://www.formedit.fr>

Lavoisier SAS, 145 rue de Provigny, 94236 Cachan Cedex
Telephone: + 33 1 47 40 67 02 • Fax +33 1 47 40 67 02
Email: romuald.verrier@lavoisier.fr • Web site: <http://www.lavoisier.fr>

GERMANY

UNO-Verlag, Vertriebs- und Verlags GmbH, Am Hofgarten 10, D-53113 Bonn
Telephone: + 49 228 94 90 20 • Fax: +49 228 94 90 20 or +49 228 94 90 222
Email: bestellung@uno-verlag.de • Web site: <http://www.uno-verlag.de>

HUNGARY

Librotrade Ltd., Book Import, P.O. Box 126, H-1656 Budapest
Telephone: +36 1 257 7777 • Fax: +36 1 257 7472 • Email: books@librotrade.hu

INDIA

Allied Publishers Group, 1st Floor, Dubash House, 15, J. N. Heredia Marg, Ballard Estate, Mumbai 400 001,
Telephone: +91 22 22617926/27 • Fax: +91 22 22617928
Email: alliedpl@vsnl.com • Web site: <http://www.alliedpublishers.com>

Bookwell, 2/72, Nirankari Colony, Delhi 110009
Telephone: +91 11 23268786, +91 11 23257264 • Fax: +91 11 23281315
Email: bookwell@vsnl.net

ITALY

Libreria Scientifica Dott. Lucio di Biasio "AEIOU", Via Coronelli 6, I-20146 Milan
Telephone: +39 02 48 95 45 52 or 48 95 45 62 • Fax: +39 02 48 95 45 48
Email: info@libreriaaeiou.eu • Website: www.libreriaaeiou.eu

JAPAN

Maruzen Company, Ltd., 13-6 Nihonbashi, 3 chome, Chuo-ku, Tokyo 103-0027
Telephone: +81 3 3275 8582 • Fax: +81 3 3275 9072
Email: journal@maruzen.co.jp • Web site: <http://www.maruzen.co.jp>

REPUBLIC OF KOREA

KINS Inc., Information Business Dept. Samho Bldg. 2nd Floor, 275-1 Yang Jae-dong SeoCho-G, Seoul 137-130
Telephone: +02 589 1740 • Fax: +02 589 1746 • Web site: <http://www.kins.re.kr>

NETHERLANDS

De Lindeboom Internationale Publicaties B.V., M.A. de Ruyterstraat 20A, NL-7482 BZ Haaksbergen
Telephone: +31 (0) 53 5740004 • Fax: +31 (0) 53 5729296
Email: books@delindeboom.com • Web site: <http://www.delindeboom.com>

Martinus Nijhoff International, Koraaalrood 50, P.O. Box 1853, 2700 CZ Zoetermeer
Telephone: +31 793 684 400 • Fax: +31 793 615 698
Email: info@nijhoff.nl • Web site: <http://www.nijhoff.nl>

Swets and Zeitlinger b.v., P.O. Box 830, 2160 SZ Lisse
Telephone: +31 252 435 111 • Fax: +31 252 415 888
Email: infoho@swets.nl • Web site: <http://www.swets.nl>

NEW ZEALAND

DA Information Services, 648 Whitehorse Road, MITCHAM 3132, Australia
Telephone: +61 3 9210 7777 • Fax: +61 3 9210 7788
Email: service@dadirect.com.au • Web site: <http://www.dadirect.com.au>

SLOVENIA

Cankarjeva Zalozba d.d., Kopitarjeva 2, SI-1512 Ljubljana
Telephone: +386 1 432 31 44 • Fax: +386 1 230 14 35
Email: import.books@cankarjeva-z.si • Web site: <http://www.cankarjeva-z.si/uvoz>

SPAIN

Diaz de Santos, S.A., c/ Juan Bravo, 3A, E-28006 Madrid
Telephone: +34 91 781 94 80 • Fax: +34 91 575 55 63
Email: compras@diazdesantos.es, carmela@diazdesantos.es, barcelona@diazdesantos.es, julio@diazdesantos.es
Web site: <http://www.diazdesantos.es>

UNITED KINGDOM

The Stationery Office Ltd, International Sales Agency, PO Box 29, Norwich, NR3 1 GN
Telephone (orders): +44 870 600 5552 • (enquiries): +44 207 873 8372 • Fax: +44 207 873 8203
Email (orders): book.orders@tso.co.uk • (enquiries): book.enquiries@tso.co.uk • Web site: <http://www.tso.co.uk>

On-line orders

DELTA Int. Book Wholesalers Ltd., 39 Alexandra Road, Addlestone, Surrey, KT15 2PQ
Email: info@profbooks.com • Web site: <http://www.profbooks.com>

Books on the Environment

Earthprint Ltd., P.O. Box 119, Stevenage SG1 4TP
Telephone: +44 1438748111 • Fax: +44 1438748844
Email: orders@earthprint.com • Web site: <http://www.earthprint.com>

UNITED NATIONS

Dept. I004, Room DC2-0853, First Avenue at 46th Street, New York, N.Y. 10017, USA
(UN) Telephone: +800 253-9646 or +212 963-8302 • Fax: +212 963-3489
Email: publications@un.org • Web site: <http://www.un.org>

UNITED STATES OF AMERICA

Bernan Associates, 4501 Forbes Blvd., Suite 200, Lanham, MD 20706-4346
Telephone: 1-800-865-3457 • Fax: 1-800-865-3450
Email: customercare@bernan.com • Web site: <http://www.bernan.com>

Renouf Publishing Company Ltd., 812 Proctor Ave., Ogdensburg, NY, 13669
Telephone: +888 551 7470 (toll-free) • Fax: +888 568 8546 (toll-free)
Email: order.dept@renoufbooks.com • Web site: <http://www.renoufbooks.com>

Orders and requests for information may also be addressed directly to:

Marketing and Sales Unit, International Atomic Energy Agency

Vienna International Centre, PO Box 100, 1400 Vienna, Austria
Telephone: +43 1 2600 22529 (or 22530) • Fax: +43 1 2600 29302
Email: sales.publications@iaea.org • Web site: <http://www.iaea.org/books>

**TECHNETIUM-99M RADIOPHARMACEUTICALS: STATUS AND TRENDS****IAEA Radioisotopes and Radiopharmaceuticals Series No. 1**

STI/PUB/1405 (360 pp.; 2009)

ISBN 978-92-0-103509-7

Price: €52.00

CYCLOTRON PRODUCED RADIONUCLIDES:**GUIDELINES FOR SETTING UP A FACILITY****Technical Reports Series No. 471**

STI/DOC/010/471 (213 pp.; 2009)

ISBN 978-92-0-103109-9

Price: €45.00

THERAPEUTIC RADIONUCLIDE GENERATORS:**⁹⁰SR/⁹⁰Y AND ¹⁸⁸W/¹⁸⁸RE GENERATORS****Technical Reports Series No. 470**

STI/DOC/010/470 (233 pp.; 2009)

ISBN 978-92-0-111408-2

Price: €45.00

CYCLOTRON PRODUCED RADIONUCLIDES:**PHYSICAL CHARACTERISTICS AND PRODUCTION METHODS****Technical Reports Series No. 468**

STI/DOC/010/468 (279 pp.; 2009)

ISBN 978-92-0-106908-5

Price: €52.00

TECHNETIUM RADIOPHARMACEUTICALS:**MANUFACTURE OF KITS****Technical Reports Series No. 466**

STI/DOC/010/466 (202 pp.; 2008)

ISBN 978-92-0-100408-6

Price: €50.00

CYCLOTRON PRODUCED RADIONUCLIDES:**PRINCIPLES AND PRACTICE****Technical Reports Series No. 465**

STI/DOC/010/465 (230 pp.; 2008)

ISBN 978-92-0-100208-2

Price: €45.00

COMPARATIVE EVALUATION OF THERAPEUTIC**RADIOPHARMACEUTICALS****Technical Reports Series No. 458**

STI/DOC/010/458 (310 pp.; 2007)

ISBN 92-0-115106-3

Price: €56.00

LABELLING OF SMALL BIOMOLECULES**USING NOVEL TECHNETIUM-99M CORES****Technical Reports Series No. 459**

STI/DOC/010/459 (312 pp.; 2007)

ISBN 92-0-101607-7

Price: €70.00

TRENDS IN RADIOPHARMACEUTICALS (2 volumes)

STI/PUB/1294 (Vol. 1: 408 pp.; Vol. 2: 464 pp.; 2007)

ISBN 92-0-101707-3

Price: €120.00

This book provides information on the production and processing of four important long lived parent radionuclides, ^{68}Ge , ^{82}Sr , ^{90}Sr and ^{188}W , used for the preparation of generators for nuclear medicine applications such as positron emission tomography and therapy. It includes descriptions of the production routes for and process chemistry of the selected parent radionuclides, including relevant separation approaches. Information on use of the generator system and on physical and chemical characteristics is also provided.

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA
ISBN 978-92-0-101110-7
ISSN 2077-6462