



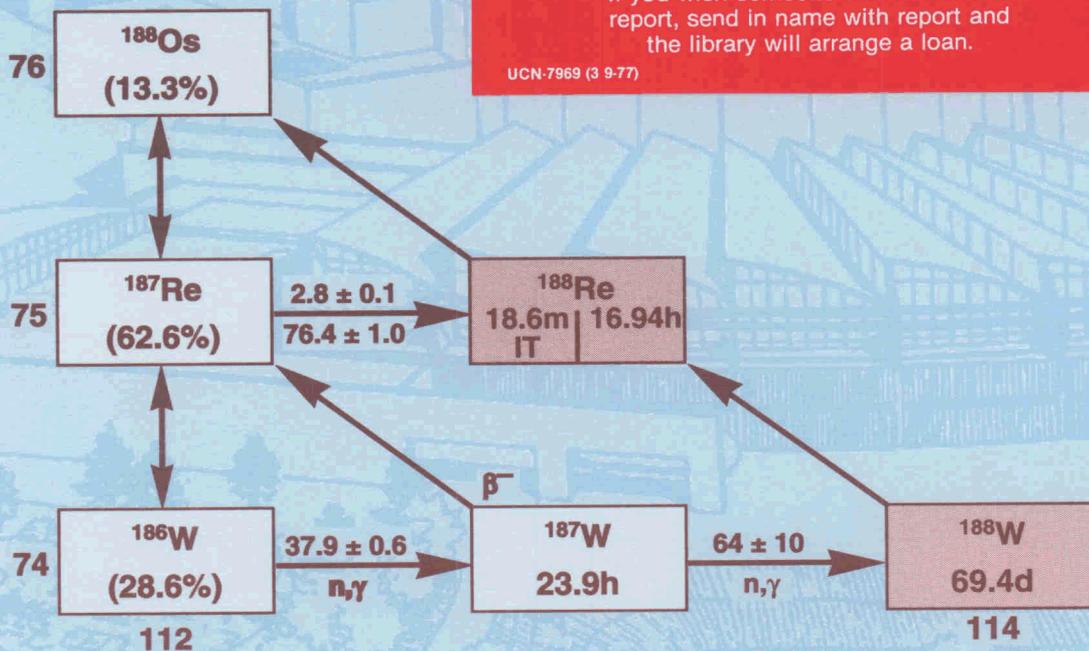
Projected Medical Radioisotope Production Capabilities of the Advanced Neutron Source (ANS)

A Supplement to:
Production Capabilities in U. S. Nuclear Reactors for Medical Radioisotopes

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**PROJECTED MEDICAL RADIOISOTOPE PRODUCTION
CAPABILITIES OF THE ADVANCED NEUTRON SOURCE (ANS)**

A SUPPLEMENT TO,

**PRODUCTION CAPABILITIES IN U.S. NUCLEAR REACTORS
FOR MEDICAL RADIOISOTOPES (ORNL/TM-12010)**

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Cover

The background shows the conceptual design of the Advanced Neutron Source (ANS) proposed for construction on the Oak Ridge Reservation at the Oak Ridge National Laboratory (ORNL). The foreground illustrates the tungsten-188 reactor production scheme. Tungsten-188 is the parent radioisotope for the tungsten-188/rhenium-188 biomedical generator system.

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PREFACE

This report provides a brief overview of the applications of radioisotopes in nuclear medicine, with special focus on reactor-produced radioisotopes. The principal goal is to describe the projected medical radioisotope production capabilities of the ANS which is planned for construction on the Oak Ridge Reservation at the Oak Ridge National Laboratory (ORNL). This report is being published as a supplement to an earlier report entitled "Production Capabilities in U.S. Reactors for Medical Radioisotopes" (ORNL/Technical Memorandum-12010, November 1992).

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1.0 INTRODUCTION

The United States faces an impending crisis in the availability of research reactors for neutron research and radioisotope research and production. The proposed Advanced Neutron Source (ANS) insures the availability of a state-of-the-art research reactor for the scientific community well into the next century. The ANS will provide neutrons for a wide variety of applications in materials science and structural biology, and will also represent a unique and powerful resource for production of transuranium elements and other radioisotopes which have a wide variety of scientific and industrial applications, most notably in medicine. The ANS is also considered as the replacement for the High Flux Isotope Reactor (HFIR) at the Oak Ridge National Laboratory (ORNL) and High Flux Beam Reactor (HFBR) at the Brookhaven National Laboratory (BNL). HFIR, which has the highest steady-state thermal neutron flux of any research reactor in the world ($2.0 \times 10^{15} \text{ n.s}^{-1} \cdot \text{cm}^{-2}$), began operation in 1965 and will continue operation until the turn of the century. The HFIR is currently operating at a power level of 85 megawatts (MW). The HFBR achieved criticality on October 31, 1965 and it provided a total flux of $1.6 \times 10^{15} \text{ n.s}^{-1} \cdot \text{cm}^{-2}$ at 40 megawatts. In 1982 the power level at the HFBR was increased to 60 MW, but since May 1991 this reactor has been operating at a nominal power level of 30 MW.

This report specifically focuses on the capabilities of the Advanced Neutron Source for the production of medical radioisotopes. The design of the irradiation facilities of the ANS is briefly discussed to provide an overview of this reactor. Inclusion of several hydraulic tube facilities in the ANS design will provide an opportunity for insertion and removal of target samples at any time period during normal reactor operation. The ANS complex will also include the availability of hot cell facilities for packing and shipping of irradiated targets. Radioisotope processing facilities are not in the present scope of ANS; however, several facilities are currently

available in the ORNL main complex. The reactor production of radioisotopes and uses in medicine for diagnosis and therapy are also discussed. A brief review of the status of the current availability of reactor-produced radioisotopes for medical use provides the groundwork for an overview of the projected medical radioisotope production capabilities of the ANS.

In order to realistically project the radioisotope production capabilities of the ANS, estimated ANS production yields of several medical radioisotopes of current interest are compared with the production capabilities of the ORNL HFIR. These radionuclides are currently in clinical trials, and include copper-67, tin-117m, dysprosium-166 (parent of holmium-166), platinum-195m and tungsten-188 (parent of rhenium-188). The important role the ANS will play in providing californium-252 is also reviewed. A discussion of the potential reactor production of molybdenum-99 by neutron capture of molybdenum-98 is also included. Molybdenum-99 is the parent of technetium-99m, which is the most widely used diagnostic radioisotope in nuclear medicine. It is estimated that more than 35,000 diagnostic studies are conducted in the U.S. daily with technetium-99m (nearly 13 million diagnostic tests annually). Molybdenum-99 is currently available only from a foreign manufacturer by processing of uranium fission products. The estimated high production yield of high specific activity molybdenum-99 in the ANS could make possible the routine production of molybdenum-99 by neutron capture, thus overcoming both the reliance on foreign manufacturers and avoiding the significant radioactive waste issues associated with the processing of fission products.

2.0 Medical Uses of Radioisotopes

2.1 Use of Radioisotopes in Nuclear Medicine

2.2 Diagnostic Applications

2.3 Therapeutic Applications

2.1 Use of Radioisotopes in Nuclear Medicine

Radioisotopes are widely used in the clinical specialty known as "Nuclear Medicine". Physicians are board-certified in nuclear medicine and are specialists in the administration of tissue-specific radioactive agents for diagnostic and therapeutic studies. The administration of radioisotopes to humans is regulated by the Food and Drug Administration (FDA) and the Nuclear Regulatory Commission (NRC). For these procedures, under the close supervision of medical personnel, small amounts of the radioactive agents are administered to patients, for example, by intravenous injection or inhalation. The procedures are thus non-invasive, normally proceeding with little patient discomfort. For full accreditation by the national hospital board, hospitals must either have the capability of performing routine nuclear medicine procedures (e.g. diagnostic) or have access to such facilities. There are thus thousands of facilities in the U.S. performing routine nuclear medicine procedures. It is estimated that about 35,000 diagnostic nuclear medicine procedures are performed with ^{99m}Tc -labeled agents in the U.S. daily (e.g. nearly 13 million/year). In 1992, for instance, there were approximately 3,900 hospitals in the U.S. which provided both inpatient and outpatient nuclear medicine services, and about 790 private, nonhospital-based nuclear medicine facilities. In hospitals, these procedures are usually performed in a designated Nuclear Medicine Department. Often, however, specific procedures

are performed in other departments. An example is diagnostic cardiac procedures, which are often performed in a cardiology department.

Radioisotopes are forms of elements which are unstable and change, or decay, to more stable forms. The time required for this decay can vary significantly from a fraction of a second to as long as millions of years. Radioisotopes which rapidly decay (i.e. short half-life) are usually used for medical applications. For example, technetium-99m is the most widely used radioisotope in nuclear medicine, and has a half-life of only six hours, which means that after six hours half of the radioactive technetium-99m has decayed away. During the radioactive decay process, energy is released in either the form of electromagnetic radiation (i.e. gamma rays or X-rays) or particle emission (e.g., negative electron). The X-rays and gamma rays can be detected by specialized photon-sensitive imaging devices used in nuclear medicine departments, which are known as gamma cameras. Radioisotopes which decay by particle emission have various therapeutic applications.

2.2 Diagnostic Applications

Diagnostic applications of radiopharmaceuticals (drugs approved for human use which are tagged with radioisotopes) provide unique information on organ function. This information cannot be obtained with other imaging modalities such as computerized tomography (CT), magnetic resonance imaging (MRI) or ultrasound techniques. After administration of a radiopharmaceutical, its transport, metabolism or localization within the patient can be detected with a gamma camera. The use of radioisotopes in medicine is based on this "tracer principle", where small amounts of radioactivity can be easily detected in the body to provide important and,

often, otherwise inaccessible, diagnostic information. Key diagnostic examples include specific and common procedures for all major organs, including the heart, kidneys, lungs, brain, thyroid and skeleton, and many of these agents are radiolabeled with the commercially available technetium-99m radioisotope. In addition, therapeutic applications include agents used to treat disease of the thyroid and cancer treatment.

2.3 Therapeutic Applications

For therapeutic applications, radioisotopes are used which decay by particle emission, most often by beta particle (electron) emission. In this case, the radiopharmaceutical agent is designed in the same manner to localize in the target tissue and the energy of the beta particle is adsorbed, with the goal of destroying the target cells. Classic examples include the treatment of various thyroid diseases with the iodine-131 radioisotope and surgical implantation of small radiotherapy sources into solid, non-resectable tumors (gold-198, palladium-103, californium-252, etc.).

Many of the radioisotopes which can be produced in the ANS with therapeutic applications offer potential treatments for a wide range of cancers, including cancer of the prostate, breast and cervix. It is important to note that for the treatment of cancer using therapeutic radioisotopes, the radioisotope is produced, purified and then chemically attached to a pharmaceutical agent. The radiolabeled agent (e.g. radiopharmaceutical) is administered to the patient and localizes at the tumor site, for instance, by nature of its specific properties. The pharmaceutical thus acts as a "carrier" for the radioisotope.

Currently, a major area of interest is the treatment of various types of cancer with therapeutic radioisotopes attached to antibodies ("radioimmunotherapy"). In this manner, cancer can be treated using therapeutic radioisotopes attached, for instance, to antibodies which specifically seek out and bind to tumor cells. Other therapeutic applications include treatment of arthritis of the fluid-filled joints ("radioisotope synovectomy") by injection of therapeutic radioisotopes directly into the joint space and treatment of bone pain associated with metastasis of cancer to the skeleton ("palliation"). Most of the therapeutic radioisotopes are reactor-produced, and for this reason the HFIR and ANS are important resources. Since the specificity of therapeutic agents for specific tumors is determined by the nature of the vehicle to which the radioisotope is attached, the characteristics of the radioisotopes must be "mated" or matched with advancements in other technologies.

3.0 Reactor-Production of Medical Radioisotopes

3.1 Importance of Reactors

3.2 Research Reactors in North America

3.1 Importance of Reactors

Radioisotopes are produced by two different routes in a nuclear reactor, where neutrons are continuously formed by the controlled fission of nuclear fuel. In the first case, the fuel can be processed to recover radioisotopes of interest, or a small nuclear fuel target (e.g. fissile uranium-235) can be irradiated for production of radioisotopes. This produces many different radioisotopes of medical interest. The fission approach produces large amounts of radioactive waste, however, which requires proper handling and disposal. The second, more common and practical method for reactor production of radioisotopes is by the direct neutron activation technique. In this case, samples of highly-purified specific target materials are inserted into the reactor for neutron irradiation. The irradiated target material is then processed to provide the desired radioactive product. A major and important advantage of this technique is that only very low levels of radioactive waste are usually formed, minimizing the environmental impact.

Radioisotopes produced by neutron activation in a reactor are typically "neutron-rich". The collision and absorption of neutrons by target nuclei result in an absolute increase in the neutron to proton ratio of the product nuclei. These nuclei are often unstable and decay (transmute) by decreasing the neutron to proton ratio, whereby a neutron is transformed to a proton plus an electron with a release of energy. In general, many reactor-produced radioisotopes decay with

the emission of beta particles and are of interest for a number of therapeutic applications. Although it is difficult to predict which radioisotopes will be of major interest in 5 or 10 years, our overview of current research and trends provides a good projection of what one may expect.

3.2 Research Reactors in North America

The projected annual U.S. sales of radioisotopes from two recent studies have clearly illustrated that the anticipated growth of FDA-approved commercial radiopharmaceuticals will be in the area of therapeutic agents.^{2,3} An important projection from this market analysis is that the principal growth in U.S. radiopharmaceutical sales is projected to be in the area of cancer detection and therapy. Since most of the therapeutic radionuclides are reactor-produced, the projected market growth potentially represents an important role for the ANS to provide reactor-produced therapeutic radioisotopes for research applications and potential commercial distributions.

Although there are a variety of university reactors and reactors at the Department of Energy (DOE) facilities, the only two reactors currently available in the U.S. for routine service irradiations for production of medical radioisotopes are the High Flux Isotope Reactor (HFIR) at the Oak Ridge National Laboratory (ORNL) and the Missouri University Research Reactor (MURR). It should be pointed out that several other DOE reactors had the potential for the routine production of medical radioisotopes, but were not designed with the appropriate target irradiation and handling facilities. These reactors include the Fast Flux Test Facility (FFTF) in Hanford, Washington, which recently has been taken out of service and the Advanced Test Reactor (ATR) in Idaho. The only other current source of reactor-produced radioisotopes in

North America is from Nordion, Inc., in Canada.

4.0 Description of ANS Facilities for Medical Radioisotope Production

The radioisotope production facilities of the ANS are summarized in Table 4.1, and consist of three hydraulic tubes and four vertical holes. A fourth hydraulic tube, with a primary role in transuranium element production, may also be available. Each hydraulic tube is capable of the simultaneous irradiation of nine capsules with on-line access at any time. The maximum sample volume per capsule is $\sim 1.26 \text{ cm}^3$. The designed peak heat flux capability of each of the hydraulic tubes is $\sim 1.75 \text{ MW/m}^2$. In contrast, the HFIR has a single hydraulic tube which is used quite extensively for the production of medical radioisotopes. The design of the ANS hydraulic tubes is identical to the HFIR design in terms of capsule capacity. Therefore, from the standpoint of physical capacity, the ANS has triple the hydraulic capacity of the HFIR. In addition, the designed peak heat flux capability of the ANS hydraulic tubes is a factor of 6 greater than what is currently available in the HFIR. The ANS peak heat flux capability will allow six times the loading of the HFIR for those targets whose loading is limited by heat flux (for example, fissionable isotopes). An expanded view of the ANS radioisotope production facilities is schematically shown in Figure 2.1. A three-dimensional view of the radioisotope production facilities is shown in Figure 2.2. In this figure, most other reflector vessel components are removed for clarity.

An important parameter for consideration in radioisotope production is sample (target) heating due to interactions with neutrons and gamma-induced charged particles (plus decay products). In the case of certain radioisotopes, the sample heating (commonly referred to as

gamma heating) may limit the sample loading capacity. In the ANS, the much higher peak flux capability relative to the HFIR will substantially reduce this potential limitation. However, the ANS, by virtue of its design criteria, further mitigates the impact of sample heating on loading capacity.

The ANS hydraulic tubes HT-1 and HT-3, which are located the furthest from the core, have aluminum heating rates lower than that of the HFIR hydraulic tube by more than an order of magnitude. The heating rate value for HT-4, which is closer to the core, is ~55% lower than that in the HFIR. Hydraulic tube HT-2, closest to the core, has a projected heating rate value which is ~20% lower than that in the HFIR. While heating rates are isotope-specific, the aluminum heating rates are reasonable indicators. In addition, the bulk of a hydraulic tube capsule is aluminum, and a reduction in the heating rate allows for higher sample loading.

Among the parameters (e.g., physical capacity, radiation-induced heat generation, and heat flux) affecting radioisotope production, the flux of thermal neutrons (thermal flux) is the most critical. The magnitude of the thermal flux, in general, determines the specific radioisotope production rate. Radioisotopes that are produced by multiple neutron captures are very sensitive to the level of the thermal flux. A higher thermal flux will generally lead to a substantial increase in the production rate of most radioisotopes.

Table 4.1 ANS IRRADIATION FACILITIES

Facility type (number)	Radius (mm)	Inside diam. (mm)	Length (mm)	Sample volume (cc)	Average thermal neutron flux $10^{15} \text{ n.cm}^{-2}.\text{s}^{-1}$	Access	Primary/secondary use
Hydraulic tube-2 (1)	310	14	585	12 (9 rabbits)	3.1	On-line	Transuranium/ isotope production
Hydraulic tube-4 (1)	380	14	585	12 (9 rabbits)	4.6	On-line	Isotope production
Hydraulic tube (straight) (2)	1064	14	585	12 (9 rabbits)	1.2	On-line	Isotope production
Vertical tube (4)	1384	32	2000	1000	0.5	On-line	Isotope production
Transuranium targets (30)	195		500	16	1.9	Refueling (20 d)	Transuranium/ isotope production
Slant hole (2)	330	48	300	500	5	Refueling (20 d)	Material irradiation
In-core instrumented capsule (5)	135	48	500	800	1.5	Refueling (20 d)	Material irradiation/ isotope production
In-core non-instrumented capsule (5)	135	548	500	800	1.5	Refueling (20 d)	Material irradiation/ isotope production

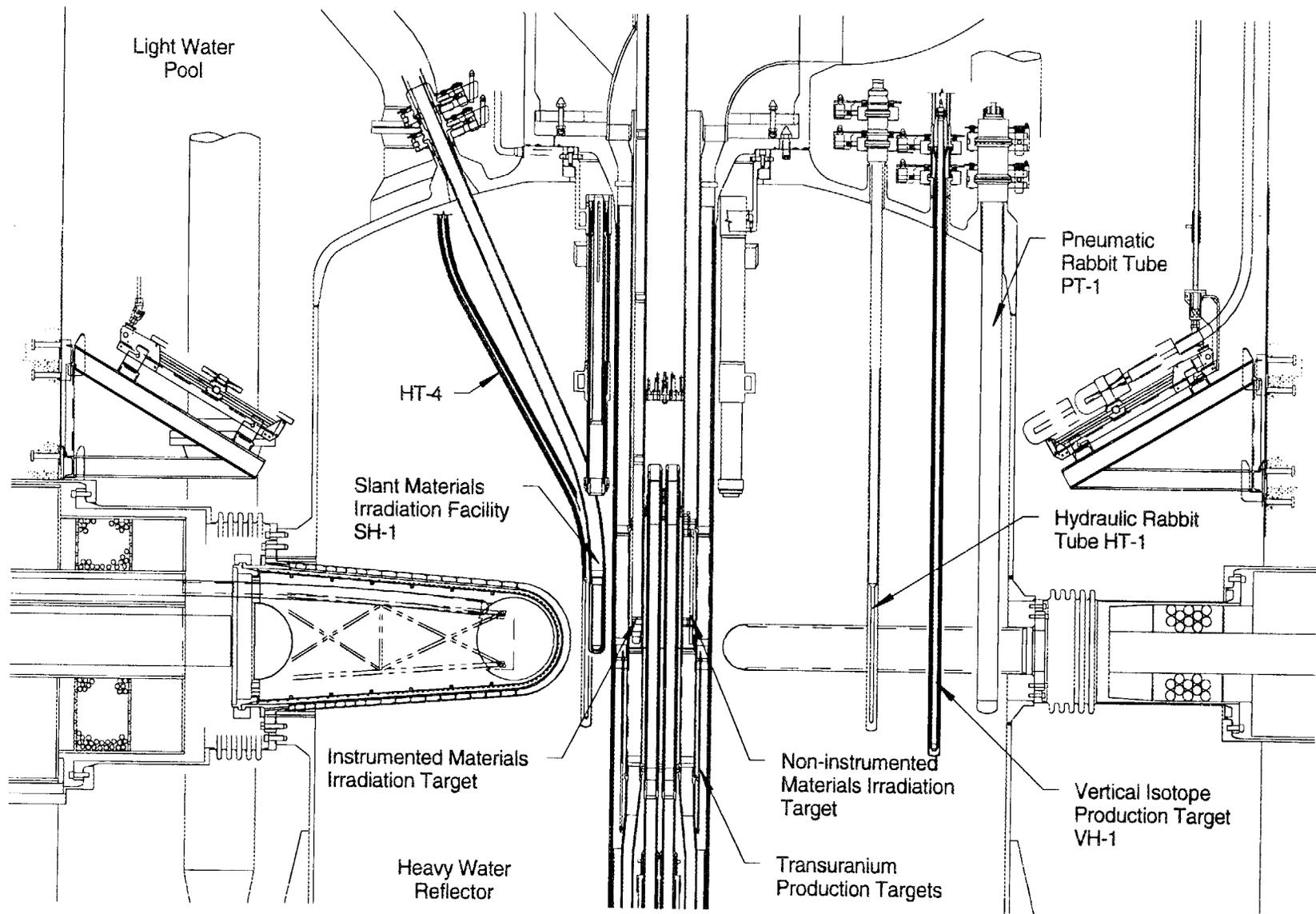


Figure 4.1. An expanded view of the ANS radioisotope production facilities

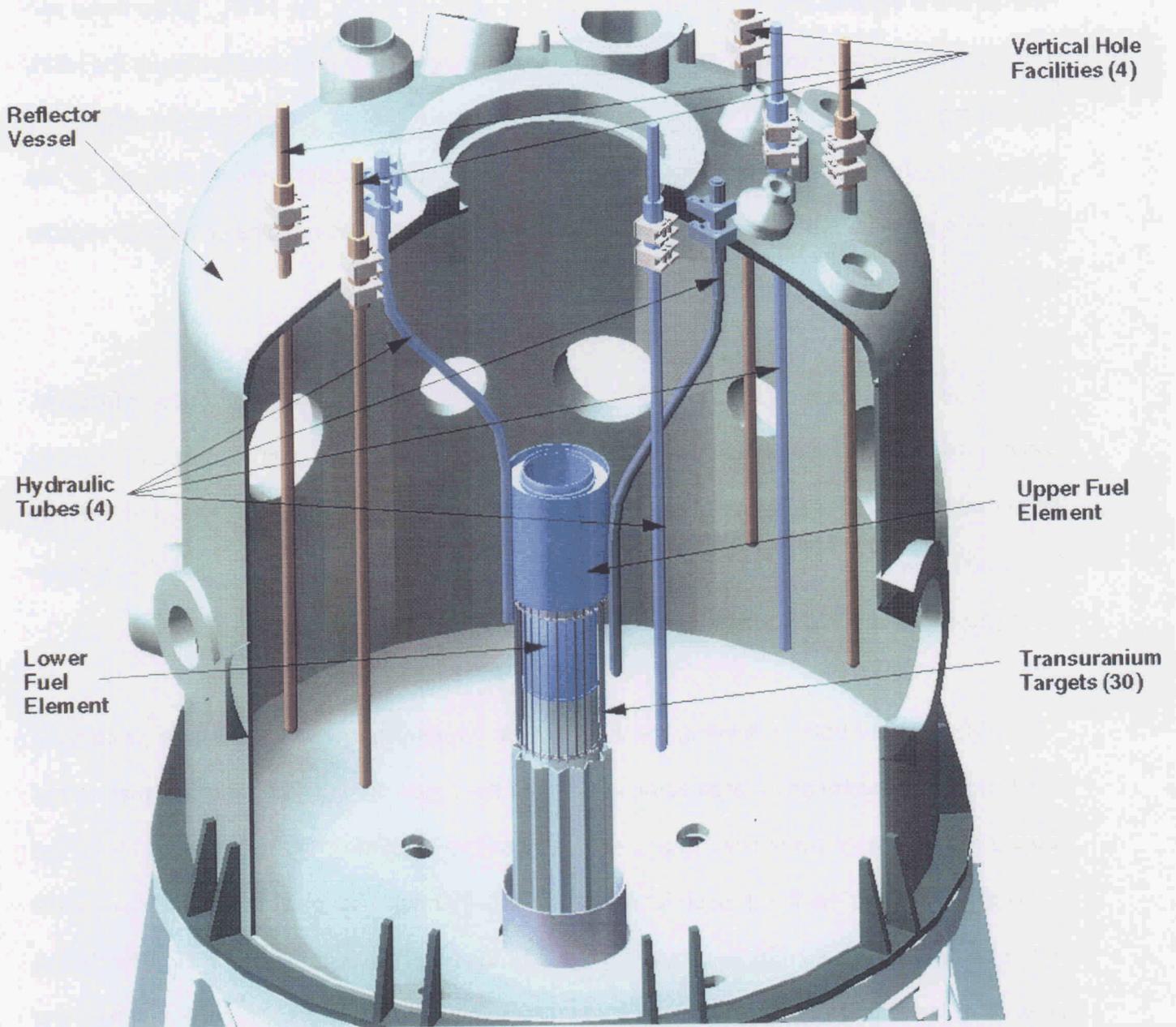


Figure 4.2. Radioisotope Production Facilities of the ANS.

(other reflector vessel components are removed for clarity)

Hydraulic tube HT-4 has a peak thermal flux ~2 times greater than what is available at the HFIR and the volume-averaged thermal flux is a factor of ~2.2 greater. From a thermal flux standpoint, the HT-4 facility alone more than doubles the existing capability at the HFIR. The other two hydraulic tubes, HT-1 and HT-3, have peak thermal fluxes ~50% of that available at HFIR and the volume-averaged thermal fluxes are ~60% of that at the HFIR. While these two tubes do not match or exceed the characteristics of the one existing hydraulic tube at the HFIR, the thermal flux exceeds 10^{15} n.cm⁻².s⁻¹. Currently there are no other reactors which have hydraulic tube facilities with these characteristics. Under consideration, however, is the engineering feasibility of relocating the HT-1 and HT-3 hydraulic tube facilities of the ANS in order to achieve a higher thermal flux.

The hydraulic tube HT-2, which is a part of the ANS transuranium production facilities, can be used for general radioisotope production if required. The use of HT-2 will be dependent on availability and/or the critical nature of the specific radioisotope mission. The peak thermal flux of HT-2 is ~1.8 times greater than the peak thermal flux at the HFIR, and the volume-averaged thermal flux is ~1.5 times greater.

The vertical hole facilities in the ANS are the primary general radioisotope production facilities for the irradiation of large samples, and for the production of radioisotopes that do not require the highest thermal flux. These four facilities are located on the same radius from the core centerline, and the flux in each facility is primarily thermal. The peak thermal flux is ~75 % of the best holes in the HFIR and exceeds those of the outer facilities in the HFIR. The design peak heat flux capability in the vertical holes is equivalent to the capability in the HFIR. The aluminum heating rate is extremely low and should have minimal impact on sample capacity. Sample volume per facility ranges from 285-710 cm³, depending on the desired thermal flux

profile. The most important and unique features are that each hole will be independently cooled and will have on-line access capability.

The ability to charge and discharge samples on demand will allow for greater optimization of isotope irradiations and increased flexibility in production schedules. No other reactor, including the HFIR, has this capability. The HFIR does have a larger total available sample volume in the reflector positions, however, than the current ANS design. Demand projections and reactor head restrictions resulted in the design of the four vertical holes. Consideration is being given to increasing the sample volume of each hole, although some penalty in loss of heat flux capability may result.

Radioisotopes can also be produced in other positions or facilities within the ANS that are not considered as part of the general radioisotope production facilities. The first facility is the transuranium target facility (TTF); this facility has the same sample volume and number of targets as the existing HFIR flux trap positions and it exceeds the HFIR peak heat flux capability. The thermal flux in ANS is ~65% of that of HFIR, and the resonance flux is 3-4 times greater than in the HFIR. The fast neutron flux, essential to the production of radioisotopes via threshold reactions, is nearly twice that of the HFIR flux trap. A number of medical and other radioisotopes are produced in this manner, and the higher fast flux in the ANS will substantially increase their production rates relative to the HFIR. The second ANS facility is the materials irradiation facility, which is located inside the upper ANS core. No comparable facility exists at the HFIR. This facility has a lower thermal flux than the transuranium production facility, but has a somewhat higher fast neutron flux. This facility will also be very valuable in the production of radioisotopes via threshold reactions. Radioisotope production in both these facilities will depend on availability and the importance of the production mission.

5.0 The ANS and Medical Radioisotope Research and Production

5.1 Key Examples Illustrating ANS Capabilities

5.1.1 Molybdenum-99 (Parent of Technetium-99m)

5.1.2 Tungsten-188 (Parent of Rhenium-188)

5.1.3 Platinum-195m

5.1.4 Tin-117m

5.1.5 Dysprosium-166 (Parent of Holmium-166)

5.1.6 Copper-67

5.1.7 Californium-252 and Other Transuraniums

5.2 Comparison Summary

5.1 Key Examples Illustrating ANS Capabilities

Any radioisotope that is, or can be, produced by a nuclear reactor can be produced by the ANS. In general, higher levels and higher specific activity (i.e. units of radioactivity per mass of target material; curies/gram) products can be produced by the ANS because of the greatly increased neutron flux.

For production of useful quantities of many medical radioisotopes of current or projected interest, the highest possible flux is required. For practical purposes high neutron flux is necessary for the production of long-lived radioisotopes and for the preparation of high specific activity radioisotopes. High flux is required, in particular, for production of those radioisotopes which are produced by multiple neutron capture where the production yields are an exponential function of the neutron flux. An example of a radioisotope for therapy produced by single

neutron capture is rhenium-186, which is of current interest for treatment of bone pain associated with cancer and for tumor therapy with antibodies (See Appendix, Table 8.1). The highest specific activity possible is required for radiolabeling tumor-specific antibodies. Key examples of double neutron capture reactions are the production of tungsten-188 and dysprosium-166, which are described later. It is also important to stress, however, not only which radioisotopes the ANS may produce in comparison to other reactors, but also what advantages the ANS has in comparison to other reactors for the efficient production of radioisotopes of medical interest. Several key examples which are of current major interest, include the production of molybdenum-99, tungsten-188, which is of widespread interest for the tungsten-188/rhenium-188 generator, and rhenium-186. The latter two are currently of broad interest and expected to generate commercial interest in the U.S. (See Appendix, Tables 8.1-8.3).

Because radioisotope production is dependent on radioisotope-specific properties, it is not possible to assign a single value to the efficiency or power of radioisotope production in the ANS relative to that of the HFIR. Taking into account several aspects of the ANS design, however, it is possible to compare the projected production of specific radioisotopes in the ANS and HFIR. These factors include the four-fold increase in physical capacity of the ANS. In addition, the factor of 2 increase in the thermal flux for hydraulic tube positions # 2 and # 4 and the factor of 6 increase in design peak heat flux capability of the ANS are important. Also, because of the significant decreases in aluminum heating rates, the ANS is expected to be more powerful than the HFIR by a factor of 4 to 10 for radioisotope production in the hydraulic tube positions. To illustrate the increased capability of the ANS for production, the following sections compare expected production rates between the ANS and HFIR of several medical radioisotopes of current or expected interest. These include molybdenum-99, which is the parent of technetium-99m, the most widely used diagnostic radioisotope in nuclear medicine. In addition,

comparative production rates for tungsten-188 (the parent of rhenium-188), dysprosium-166 (the parent of holmium-166), copper-67, platinum-195m and tin-117m are also included. A summary of the potential applications of these radioisotopes is given in Table 5.1. Finally, the capabilities of the ANS for production of the transuranium element, californium-252, is also provided.

The nuclear reactions for production of some of these radioisotopes are summarized in Table 5.2. These reactions also represent the general types of nuclear reactions occurring with reactor neutrons. In Figures 5.1-5.6, the production curves of the above radioisotopes are plotted as a function of the irradiation period. With the exception of copper-67, comparisons are made between two hydraulic tube positions of the ANS (ANS hydraulic tube positions HT-2 and HT-4) and the hydraulic tube positions of the HFIR (HFIR-HT). For copper-67, the production estimates are compared in the ANS "TTF" and "HT-2" positions, and the HFIR hydraulic tube irradiation facilities described later. Copper-67 is primarily produced by fast neutrons and is a good example of a threshold reaction.

Table 5.1. Examples of Reactor-Produced Radioisotopes Currently Under Clinical Trials^a

Radionuclide	Half-life	Example of Applications and Comments	Reference
Copper-67	61.9 h	Labeled antibody for soft tissue tumor therapy	1
Technetium-99m	6.0 h	Labeled drugs and particles for various diagnostic applications. High specific activity is produced via the ⁹⁹ Mo/ ^{99m} Tc generator system.	
Tin-117m	13.6 d	^{117m} Sn-"DTPA" as palliative agent for painful skeletal metastases	2
Holmium-166	26.4 h	Labeled antibodies for tumor therapy and as labeled particles for treatment of rheumatoid arthritis and cancer of liver. High specific activity is produced through decay of ¹⁶⁶ Dy/ ¹⁶⁶ Ho generator system.	3,4
Platinum-195m	4.0 d	Pharmacokinetics of antitumor drugs (e.g. "cis-platinum")	5
Rhenium-188	17.0 h	As labeled antibody for tumor therapy and as Re-DMSA agent for treatment of medullary thyroid carcinoma and bone metastases. High specific activity is produced via ¹⁸⁸ W/ ¹⁸⁸ Re generator system.	6,7

^aAlthough widely used clinically, technetium-99m is included in this table for comparative purposes

Table 5.2. Nuclear Reactions for Production of Copper-67 (^{67}Cu), Tin-117 ($^{117\text{m}}\text{Sn}$), Dysprosium-166 (^{166}Dy), Platinum-195m ($^{195\text{m}}\text{Pt}$) and Tungsten-188 (^{188}W).

Product Radionuclide	Half-Life	Target Nuclide Nuclear Reaction	Comments
^{67}Cu	61.9 h	$^{67}\text{Zn}[n,p]^{67}\text{Cu}$	
^{99}Mo	2.75 d	$^{98}\text{Mo}[n,\gamma]^{99}\text{Mo}^{\text{a}}$	Parent of $^{99\text{m}}\text{Tc}$
$^{117\text{m}}\text{Sn}$	13.9 d	$^{116}\text{Sn}[n,\gamma]^{117\text{m}}\text{Sn}$	
^{166}Dy	81.5 h	$^{164}\text{Dy}[n,\gamma]^{165\text{g}}\text{Dy}(2.35\text{ h})[n,\gamma]^{166}\text{Dy}$	Parent of ^{166}Ho
$^{195\text{m}}\text{Pt}$	4.02 d	$^{194}\text{Pt}[n,\gamma]^{195\text{m}}\text{Pt}$	
^{188}W	69 d	$^{186}\text{W}[n,\gamma]^{187}\text{W}(23.8\text{ h})[n,\gamma]^{188}\text{W}$	Parent of ^{188}Re

^a An alternative to the fission production route

Following this description of the comparison of the ANS and the ORNL High Flux Isotope Reactor (HFIR) for production of medical radioisotopes, the ANS radioisotope production facilities are discussed.

5.1.1 Molybdenum-99

Although molybdenum-99 used in the United States is produced in Canada from fission of uranium, there are distinct long-term advantages for routine production of molybdenum-99 by neutron activation of enriched molybdenum-98 targets. For fabrication of molybdenum-99/technetium-99m generators, the principal issue which differentiates fission-produced Mo-99 from neutron-activated production of molybdenum-99 is specific activity. Since the fission route produces high levels of radioactive waste, the preferred route for molybdenum-99 production would be expected to be by neutron-activation, if sufficient specific activity could be attained. With its very high neutron flux, the ANS is expected to offer the first opportunity for routine production of molybdenum-99 by neutron activation with high enough specific activity for generator fabrication. Projected production yields are summarized in Table 5.3.

A comparative method was used for calculation of the projected molybdenum-99 production yields from neutron irradiation of enriched molybdenum-98. These calculations consider the higher neutron flux of the ANS relative to the HFIR, assuming that the ANS has at least two times the thermal neutron flux of the HFIR (e.g., hydraulic tube position #4 of the ANS is expected to have a peak thermal flux which is 100% greater than the maximal flux available in the HFIR). The calculations also consider contributions for the resonance integrals (epithermal neutrons) for neutron capture by the molybdenum-98 target atoms.

Table 5.3 Projection of the ANS Production Capability of Mo-99 Produced by $^{98}\text{Mo}[n,\gamma]$ Reaction

Parameters	ANS Irradiation Positions		
	HT2	HT4	VT
Theo. yield per week (Ci/g)	2.0×10^2	1.7×10^2	1.5×10^1
Mass of Mo metal (g)	1.2×10^2	1.4×10^2	1.6×10^3
Theo. vol of Mo (cm^3)	1.2×10^1	1.3×10^1	1.6×10^2
Available Vol. (cm^3) ^b	(9) x (1.7)	(9) x (1.7)	(4) x (2×10^3)

^aCalculation is based on the current demand of 2.4×10^4 Ci/week of Mo-99 in U.S.

^b(Number of available positions) x (volume per position)

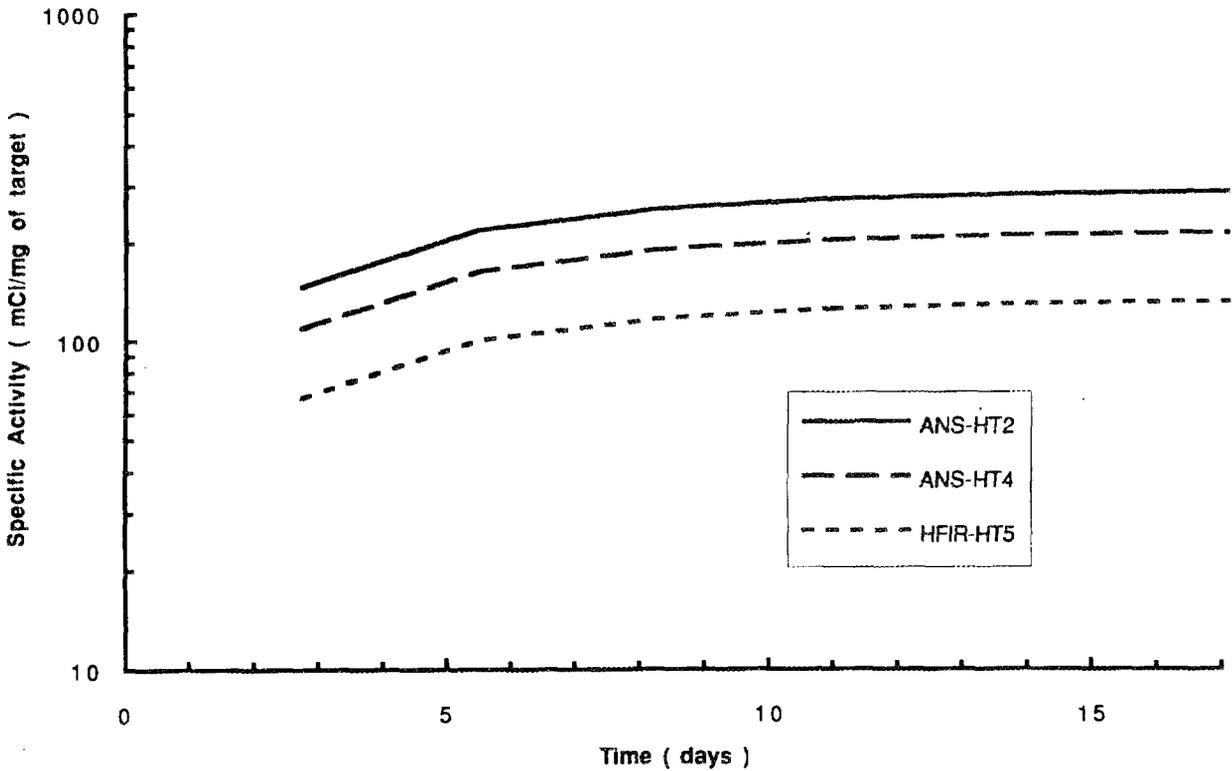


Figure 5.1. Production of molybdenum-99 via neutron capture of enriched molybdenum-98

5.1.2 Tungsten-188

Reactor-produced tungsten-188 is a radioisotope of widespread interest, since it is used to prepare a generator in which the rhenium-188 radioisotope formed from decay of the tungsten-188 can be readily obtained for attachment to therapeutic agents. The ANS is expected to produce at least 100% more of the tungsten-188 in a much shorter irradiation time compared to the HFIR. Increased production capabilities will also conserve target material and greatly reduce the unit costs of this important medical radioisotope.

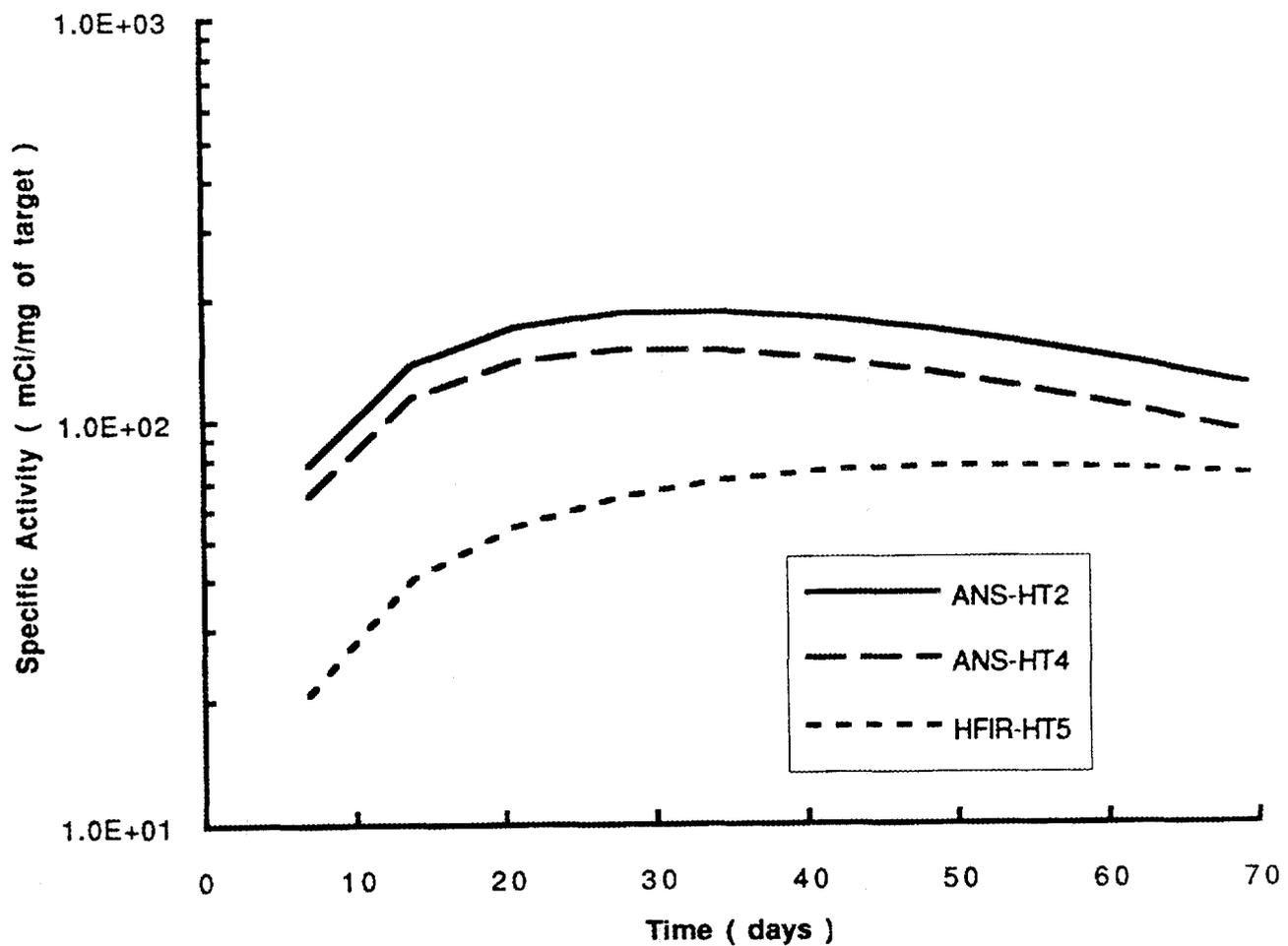


Figure 5.2. Production of Tungsten-188

5.1.3 Platinum-195m

Platinum-195m is used as a tracer for study of the pharmacokinetics of the widely used clinical antitumor drug, "cis-platinum" [5]. The production yield for ANS-HT2 is expected to be at least 50% more than yield from HFIR. Considering the very limited availability of highly enriched Pt-194 target, the increase in yield will result in conservation of the target material.

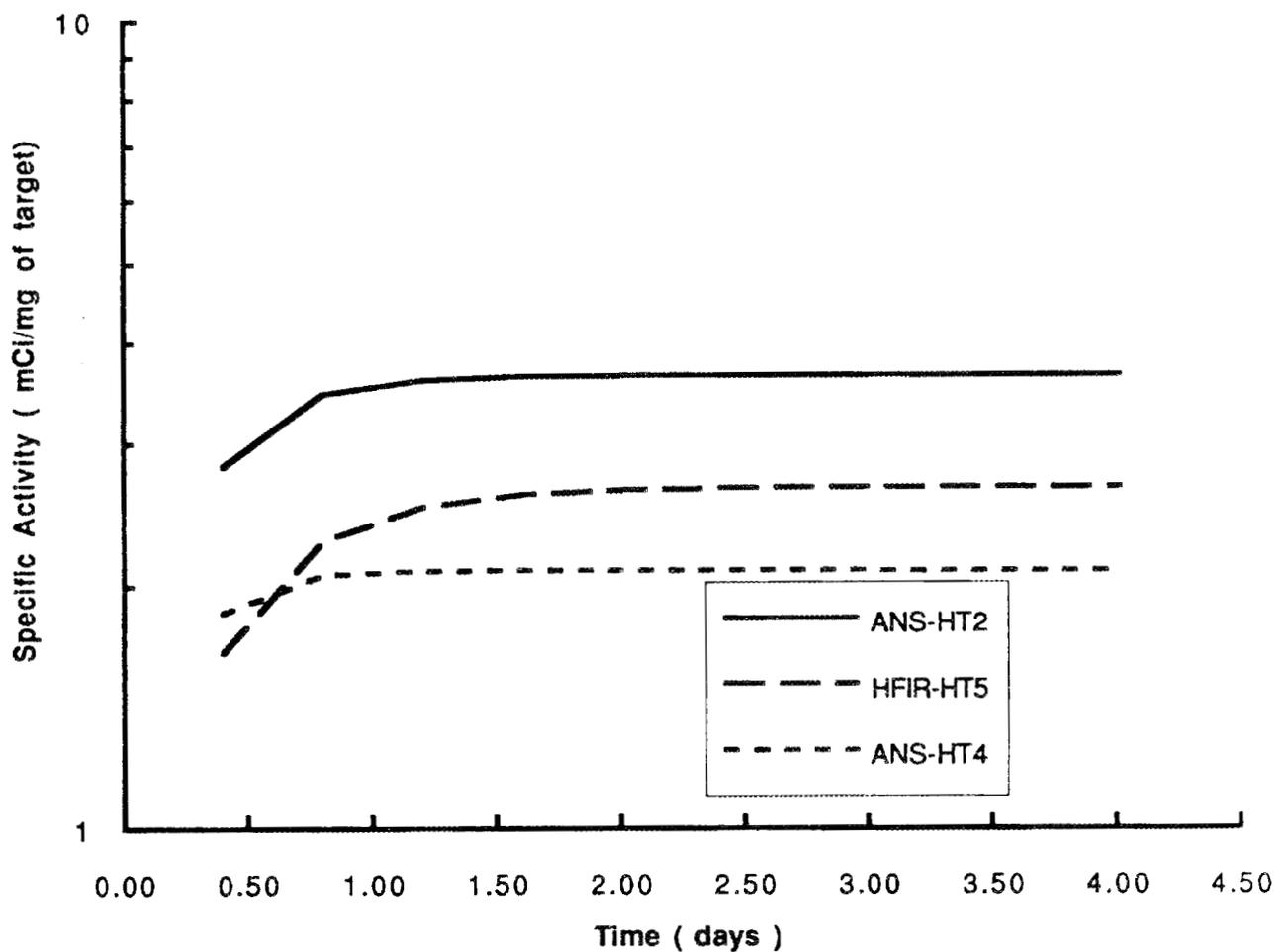


Figure 5.3. Production of Platinum-195m

5.1.4 Tin-117m

Tin-117m has recently been shown very promising results in initial clinical studies as the DTPA complex for palliative treatment of painful skeletal metastases [2]. The specific activity of tin-117m produced in ANS-HT2 and ANS-HT4 is expected to be greater than what is currently produced at HFIR by a factor of 2-3, respectively.

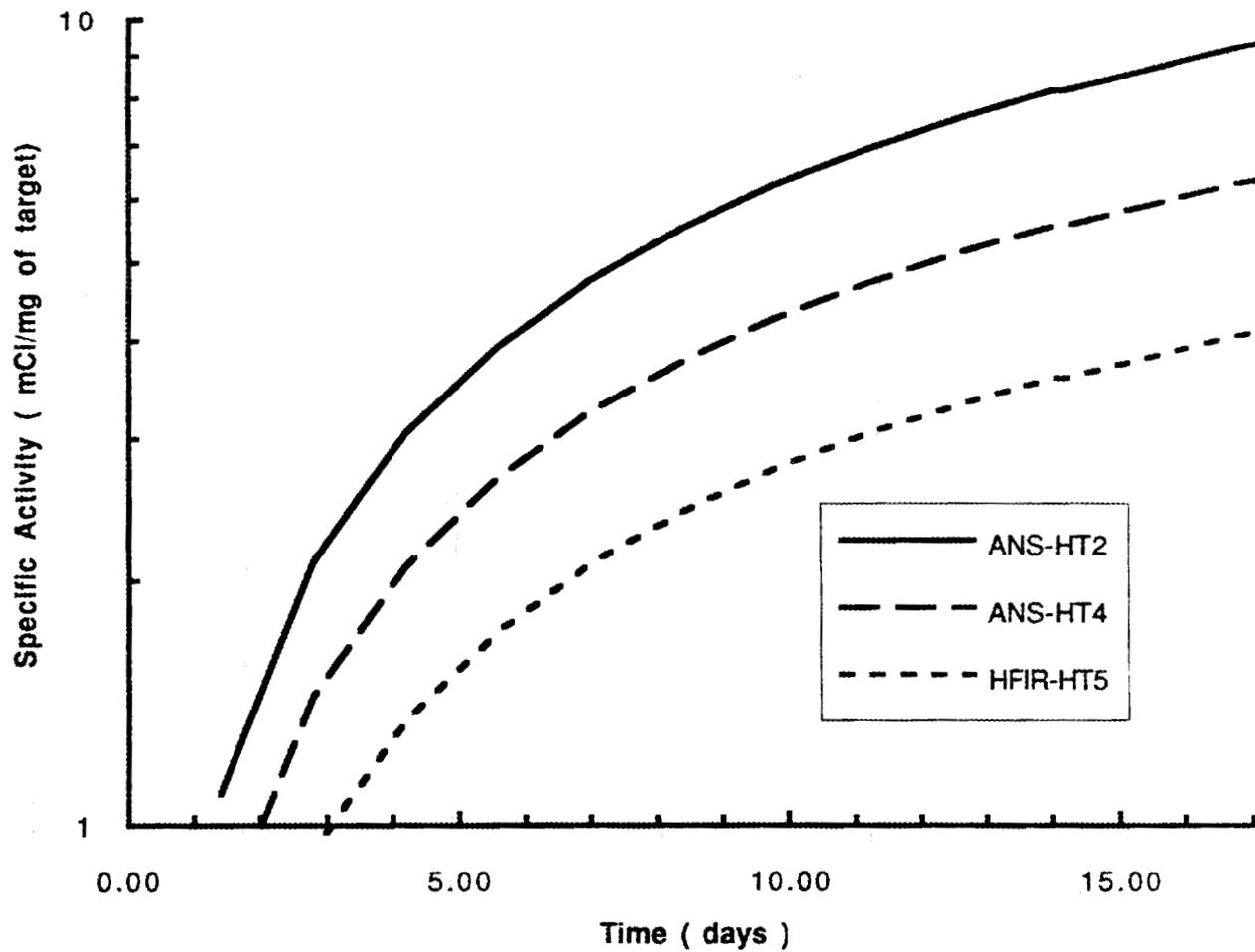


Figure 5.4. Production of Tin-117m

5.1.5 Dysprosium-166 (parent of Holmium-166)

Dysprosium-166 decays to holmium-166 and is also produced by a double neutron capture process, and is another example of the important increased production capabilities of high flux reactors such as the HFIR and ANS. Holmium-166 has applications in cancer therapy [1,3,4,6,7]. As shown below, a yield of ~ 10 Ci/mg is expected for 16 h irradiation at ANS-HT4, in comparison to a yield of ~ 5 Ci/mg from HFIR - HT5 for 30 hours of irradiation.

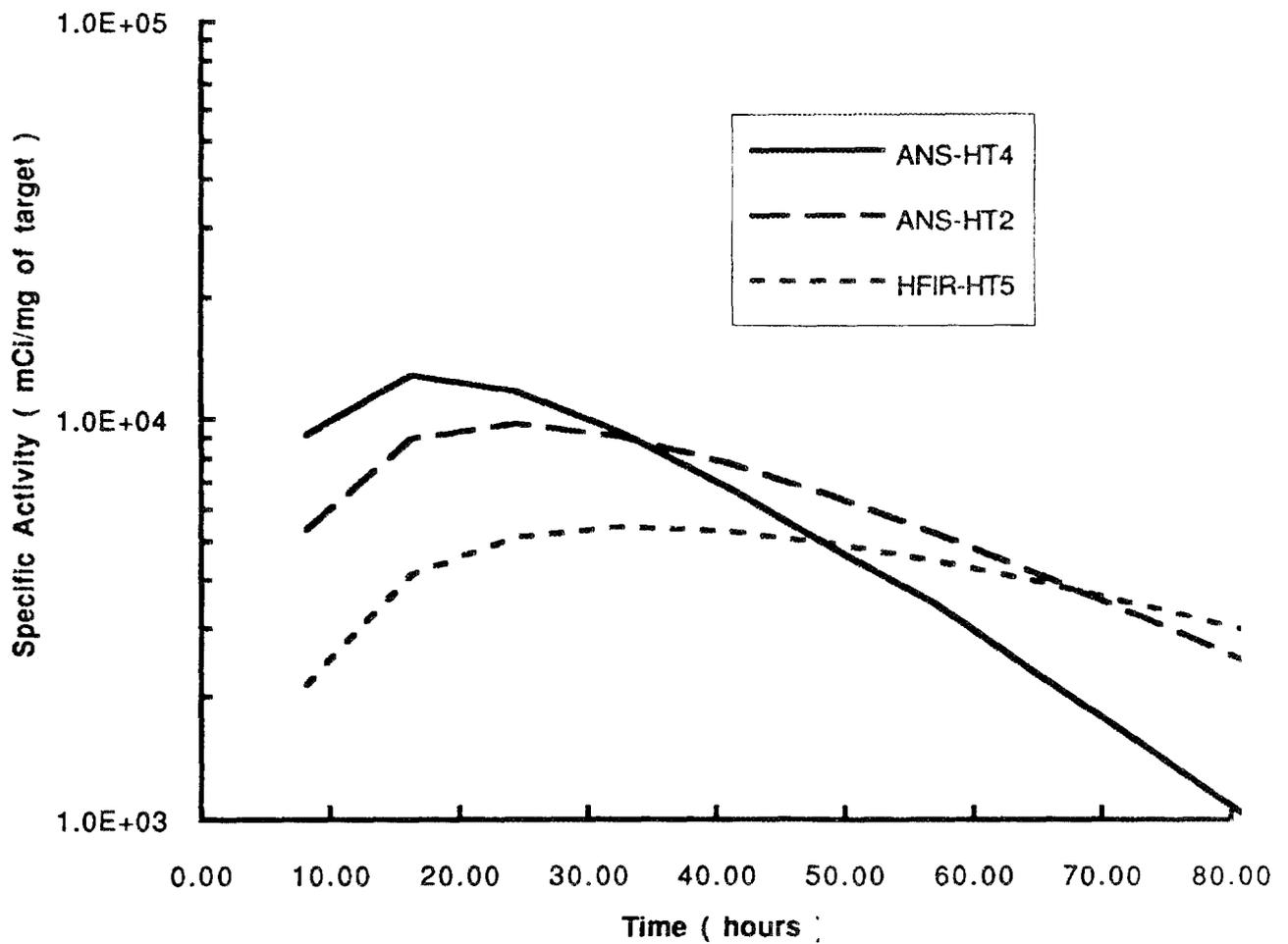


Figure 5.4. Production of Dysprosium-166

5.1.6 Copper-67

Copper-67 is under clinical evaluation for cancer of soft tissue. Fast neutrons are required for production of this radioisotope. Although expected yields of copper-67 from ANS hydraulic tube facilities are not as high as those obtained from HFIR-HT5, the ANS Transuranium Target Facilities (TTF) may be used for production of this isotope with appreciably higher yield. Copper-67 is more efficiently and less expensively produced using high energy accelerators, but because of the traditional seasonal operation of these facilities (i.e. "BLIP" at BNL and "LAMPF" at LANL), reactor production could help fill voids when this radioisotope would otherwise be unavailable.

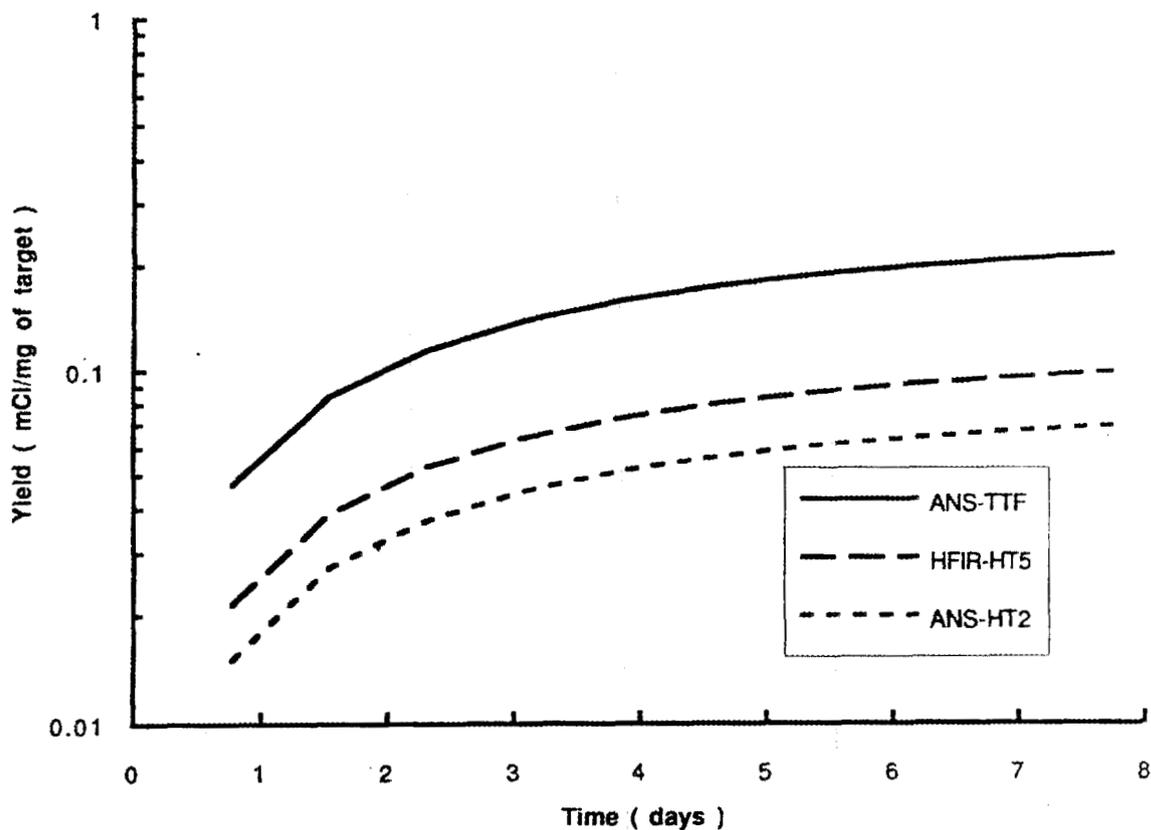


Figure 5.6. Production of Copper-67

5.1.7. Californium-252

In the past three decades there have been extensive studies of neutrons for cancer therapy. Based on purely radiobiological rationale, neutrons are more effective than conventional X-rays in overcoming the radio-resistance of cancers. Evidence from extensive basic cancer research has shown high efficacy of neutrons in treatment of radio-resistant cancers, in cases such as hypoxic tumors, rapid tumor growth and necroses in tumors. Most efforts in this field have focused on fast neutron beam therapy, where some efficacy has been found against parotid gland, prostate gland and sarcoma tumors, but with frequent side effects. Recognition of californium-252 (Cf-252) as a neutron source has provided the most successful form of neutron therapy of bulky and x-ray resistant tumors. In this approach, sealed sources of Cf-252 are implanted as seeds directly into the tumors. This form of therapy, termed "brachytherapy", delivers neutron radiation directly to the tumor and target volume and minimizes dose to adjacent normal and sensitive tissues. The methods for treatment are basically intracavitary (i.e., in body cavities) or interstitial, inserted into tissues (e.g. prostate gland or oral cavity). Californium-252 may be the only agent effective against glioblastoma multiform (brain cancer) where high efficacy has been demonstrated with twofold increase in the survival. Nearly 3,000 cancer patients have been treated to date with this technique. The cure rates for bulky, localized cervical cancers have been found to be 95% for 5 years and even for advanced cases can be 54% for 5 years. These observations have been confirmed in Japan, the former USSR and Czechoslovakia [11].

Important technological and biological applications under study are enhancement of Cf-252 dose by boron and gadolinium thermal neutron capture during brachytherapy; a teletherapy machine for body surface or boron neutron capture therapy; and Cf-252 research laboratory irradiators. The present Cf-252 centers are projected to increase from 10 in 1990 to 100 in 2001 and require 0.5-1 mg/2.5 years; and from 3 research irradiators to 10-15

irradiator/teletherapy machines by 2001. The latter will each require 25-100 mg for 5 years [11].

The current ANS design will be capable of producing 1.5 g of Cf-252 per year. This capability is equal to the production-recovery capacity of the High Flux Isotope Reactor - Radiochemical Engineering Development Center. Currently, the center is producing and recovering ~ 500 mg of Cf-252 per year.

5.2 Comparison Summary

The comparison summary for production of copper-67, tin-117m, holmium-166, platinum-195m and tungsten-188 is summarized later in Table 5.3. The comparison also includes the production yields of molybdenum-99, produced via neutron capture reaction rather than the fission reaction.

In conclusion, the ANS radioisotope production capabilities in general will equal or be superior to the radioisotope production capabilities of the HFIR. The on-line access capability of the ANS vertical hole facilities is unique and should offset, to a large degree, the larger sample capacity of the HFIR reflector positions. The capabilities of these ANS facilities will offer an increased efficiency of radioisotope production, a greater availability, an increase in optimization of production, and, as a result, conservation and efficient use of rare or expensive isotopes used in production.

Table 5.3. A Comparison Between ANS and HFIR for Production of Copper-67, Californium-252, Molybdenum-99, Tin-117m, Dysprosium-166, Platinum-195m and Tungsten-188.

Product Radionuclide	Irradiation Period	Production Yield (mCi/mg of target)			Comments
		ANS-TTF	ANS-HT2	HFIR-HT	
Copper-67	8.0 d	2.1×10^{-1}	8.0×10^{-1}	9.7×10^{-2}	Approximate Saturation Yield
		ANS-HT4	ANS-HT2	HFIR-HT(#5)	
Molybdenum-99	11.0 d	2.1×10^2	2.8×10^2	1.3×10^2	Approximate Saturation Yield
Tin-117m	17.0 d	9.2	6.3	4.1	1 ANS cycle
Dysprosium-166	16.3 h	1.3×10^4	9.4×10^3	4.3×10^3	Maximum Yield
Tungsten-188	17.0 d	1.3×10^2	1.6×10^2	4.6×10^2	1 ANS cycle
Platinum-195m	1.2 d	2.1	3.6	2.5	Saturation Yield
		ANS-TTF	HFIR-TTF		
Californium-252	1 y	1.5 mg	~ 1 mg		

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7.0 References

1. Mirzadeh, S., Schenter, R. E., Callahan, A. P. and Knapp, Jr., (Russ), F. F., "Production Capabilities in U.S. Reactors for Medical Radioisotopes," ORNL/Technical Memorandum-12010, November 1992.
2. Data from Market Intelligence Research Corporation, 1989.
3. Biomedical Business International, Report # 2740, "Cancer Management Practices, Products and Market Applications - Therapy Choices for the Late 1990's," July 1993.
4. De Nardo, G., De Nardo, S., Kukis, D., Diril, H., Suny, C., Meares, C., "Strategies for Enhancement of Radioimmunotherapy", Int. J. Radiat. Appl. Instrum. Part B, Nucl. Med. Biol., **18**, 633 (1991).
5. Atkins, H., Mausner, L. F., Cabahug, C. J., Meinken, G. E., Strub, R. E., Weber, D. A. and Srivastava, S. C., "Tin-117m(+4)DTPA: A Potential Agent for Pain Palliation for Osseous Metastases", J. Nucl. Med., **9**, 1840 (1991).
6. Mumper, R. J., Mills, B. J., Ryo, U. Y. and Jay, M., "Polymeric Microspheres for Radionuclide Synovectomy Containing Neutron-activated Holmium-166", J. Nucl. Med., **33**, 398 (1992)
7. Brown, R. F., Lindesmith, L. C. and Day, D. E., "¹⁶⁶Holmium-containing Glass for Internal Radiotherapy of Tumors", Int. J. Radiat. Appl. Instrum. Part B, Nucl. Med. Biol., **18**, 783 (1991).
8. Pil, P. M. and Lippard, S. L., "Specific Binding of Chromosomal Protein HMG1 to DNA Damaged by the Anticancer Drug Cisplatin", Science **256**, 234 (1992).
9. Griffiths, H. J., Knapp, F. F., Jr., Callahan, A. P., Chang, C. -H., Hansen, H. J. and Goldenberg, D. M., "Direct Radiolabelling of Monoclonal Antibodies with Generator-Produced Rhenium-188 for Radioimmunotherapy", Cancer Research, **51**, 4594 (1991).
10. Singh, J., Powel, A. K., Clarke, S. E. M. and Blower, P. J., "Crystal Structure and Isomerism of a Tumor Targeting Radiopharmaceutical: [ReO(dmsa)₂]", Chem. Soc. Chem. Commun., 1115 (1991).
11. Neutron Sources and Applications, D. L. Price and J. J. Rush Eds., Report of a Review Held at Oak Brook, Illinois, September 1992.

8.0 Appendix

Table 8.1. Examples of Reactor-Produced Radioisotopes Currently Used for Clinical Applications and Distributed Commercially

Radioisotope	Application
<u>Diagnostic Applications:</u>	
Molybdenum-99	Decays to technetium-99m which is the most widely used radioisotope in clinical nuclear medicine
Xenon-133	Used for lung ventilation studies
<u>Therapeutic Applications:</u>	
Californium-252	Cancer therapy
Erbium-169	Arthritis Treatment
Rhenium-186	Bone cancer and tumor therapy
Palladium-103	Treatment of prostatic cancer
Phosphorus-32/33	Cancer therapy and important Application in genome research
Strontium-89	Recently approved by the FDA for routine Clinical use to treat bone cancer
Strontium-90	Decays to yttrium-90 - used for cancer and arthritis therapy

Table 8.2. Examples of Reactor-Produced Radioisotopes With Developed Applications and Established Clinical Studies, Expected to be Commercially Marketed in the Near Future

Radioisotope	Application
<u>Diagnostic Applications:</u>	
Copper-64	Various diagnostic agents
Osmium-191	Decays to iridium-191m - used for heart function tests
Platinum-195m	Pharmakokinetic studies of antitumor agent
<u>Therapeutic Applications:</u>	
Copper-67	Cancer therapy
Dysprosium-165	Arthritis therapy
Dysprosium-166	Decays to holmium-166 for cancer therapy
Erbium-169	Arthritis therapy
Gold-199	Used for arthritis and cancer therapy
Holmium-166	Cancer therapy
Iridium-192	Cancer therapy
Rhenium-186	Cancer therapy, treatment of arthritis
Samarium-145	Treatment of ocular cancer
Samarium-153	Palliative treatment of bone cancer pain
Tin-117m	Palliative treatment of bone cancer pain
Tungsten-188	Decays to rhenium-188 for treatment of cancer and arthritis

Table 8.3. Examples of Reactor-Produced Radioisotopes Currently Under Preclinical Evaluation and Expected to Have Potential Medical Applications

Radioisotope	Application
<u>Therapeutic Applications:</u>	
Arsenic-77	Cancer therapy
Osmium-194	Decays to iridium-194 - for cancer therapy
Einsteinium-253	Antibodies for cancer therapy
Fermium-255	Antibodies for cancer therapy
Lutetium-177m	Cancer therapy
Silver-111	Cancer therapy

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