FINAL REPORT

One of Two 2008 NSAC Charges on the National Isotopes Production and Application Program

Compelling Research Opportunities using Isotopes

NSAC Isotopes Subcommittee

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April 23, 2009

The Cover: The discovery of isotopes is less than 100 years old, today we are aware of about 250 stable isotopes of the 90 naturally occurring elements. The number of natural and artificial radioactive isotopes exceeds 3200, already, and this number keeps growing every year. "Isotope" originally meant elements that are chemically identical and non-separable by chemical methods. Now isotopes can be separated by a number of methods such as distillation or electromagnetic separation.The strong colors and the small deviations from one to the other indicate the small differences between isotopes that yield their completely different properties in therapy, in nuclear science, and a broad range of other applications. The surrounding red, white and blue theme highlights the broad national impact of the US National Isotope Production and Application program.

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Executive Summary

Isotopes are vital to the science and technology base of the US economy. Isotopes, both stable and radioactive, are essential tools in the growing science, technology, engineering, and health enterprises of the 21st century. The scientific discoveries and associated advances made as a result of the availability of isotopes today span widely from medicine to biology, physics, chemistry, and a broad range of applications in environmental and material sciences. Isotope issues have become crucial aspects of homeland security. Isotopes are utilized in new resource development, in energy from bio-fuels, petrochemical and nuclear fuels, in drug discovery, health care therapies and diagnostics, in nutrition, in agriculture, and in many other areas.

The development and production of isotope products unavailable or difficult to get commercially have been most recently the responsibility of the Department of Energy's Nuclear Energy program. The President's FY09 Budget request proposed the transfer of the Isotope Production program to the Department of Energy's Office of Science in Nuclear Physics and to rename it the National Isotope Production and Application program (NIPA). The transfer has now taken place with the signing of the 2009 appropriations bill. In preparation for this, the Nuclear Science Advisory Committee (NSAC) was requested to establish a standing subcommittee, the NSAC Isotope Subcommittee (NSACI), to advise the DOE Office of Nuclear Physics. The request came in the form of two charges: one, on setting research priorities in the short term for the most compelling opportunities from the vast array of disciplines that develop and use isotopes and two, on making a long term strategic plan for the NIPA program. This is the final report to address charge 1.

NSACI membership is comprised of experts from the diverse research communities, industry, production, and homeland security. NSACI discussed research opportunities divided into three areas: 1) medicine, pharmaceuticals, and biology, 2) physical sciences and engineering, and 3) national security and other applications. In each area, compelling research opportunities were considered and the subcommittee as a whole determined the final priorities for research opportunities as the foundations for the recommendations. While it was challenging to prioritize across disciplines, our order of recommendations reflect the compelling research prioritization along with consideration of time urgency for action as well as various geo-political market issues. Common observations to all areas of research include the needs for domestic availability of crucial stable and radioactive isotopes and the education of the skilled workforce that will develop new advances using isotopes in the future. The six recommendations of NSACI reflect these concerns and the compelling research opportunities for potential new discoveries. The science case for each of the recommendations is elaborated in the respective chapters.

The six recommendations of NSACI are summarized below in order of priority:

There are compelling research opportunities using alpha-emitters in medicine. There is tremendous potential in developing far more effective treatments of cancers by the use of alpha-emitters in comparison to other radio-isotopes. Therefore, development and testing of therapies using alpha emitters are our highest priority for research isotope production for the medical field. This opportunity can be realized by a variety of alpha emitters with the highest priority given to ^{225}Ac. This priority is reinforced by the potential need for rapid action due to the 2012 deadline for downblending of current DOE stocks of ^{233}U, a procedure that would eliminate its value as a source of ^{225}Ac.

1. **Invest in new production approaches of alpha-emitters with highest priority for ^{225}Ac. Extraction of the thorium parent from ^{233}U is an interim solution that needs to be seriously considered for the short term until other production capacity can become available.**

There is strong evidence for the potential efficacy of pairs of isotopes with simultaneous diagnostic/therapeutic capabilities where damage to normal tissue is minimized and exposure to target tissue is enhanced. NSACI finds the research opportunities offered with these pairs of isotopes to be the second highest priority. Many of the short-lived diagnostic/therapeutic isotopes (2nd entry in Table 8) could be produced at existing accelerator facilities but are not widely available. We recommend the maximization of the production and availability of these isotopes domestically in the US through investments in research and coordination between existing accelerators. Increasing such coordination and R&D has the potential to improve the availability of a number of other isotopes. The panel felt that such a network could benefit all areas of basic research and applications from security to industry. This should include R&D to standardize efficient production target technology and chemistry procedures.

2. **We recommend investment in coordination of production capabilities and supporting research to facilitate networking among existing accelerators.**

The basic physical sciences and engineering group prioritized research opportunities across various disciplines and a summary of this prioritization is given in Table 9. The availability of californium, radium, and other trans-uranic isotopes are particularly important for research in nuclear physics and chemistry.

3. **We recommend the creation of a plan and investment in production to meet these research needs for heavy elements.**

Experts in the nuclear security and applications areas strongly consider the vulnerability of supply from foreign sources to be of highest priority. This concern was echoed strongly by all members of the subcommittee from medicine to basic science and engineering. Additionally,

the projected demand for ^{3}He by national security agencies far outstrips the supply. This would likely endanger supply for many other areas of basic research. While it is beyond our charge, it would be prudent for DOE/NNSA and DHS to seriously consider alternative materials or technologies for their neutron detectors to prepare if substantial increases in ^{3}He production capacity cannot be realized.

4. **We recommend a focused study and R&D to address new or increased production of ^{3}He.**

An important issue for the use of isotopes is the availability of high-purity, mass separated isotopes such as ^{236}Np for dilution mass spectrometry. The stable isotopes ^{76}Ge and ^{28}Si (^{3}He is stable but obtained from the beta-decay of ^{3}H, not by isotope separation) listed in Table 9 are needed in large quantities that present special problems. While no other individual stable isotope reached the level of the highest research priority, the broad needs for a wide range of mass-separated isotopes and the prospect of no domestic supply raised this issue in priority for the subcommittee. NSACI feels that the unavailability of a domestic supply poses a danger to the health of the national research program and to national security. The subcommittee recommends:

5. **Research and Development efforts should be conducted to prepare for the reestablishment of a domestic source of mass-separated stable and radioactive research isotopes.**

Vital to the success of all scientific endeavors is the availability of a trained workforce. While the scientific opportunities have expanded far beyond the disciplines of radiochemistry and nuclear chemistry, the availability of trained personnel remains critical to the success of research in all frontiers of basic science, homeland security, medicine, and industry. The individual research areas must make concerted efforts to invest in work-force development to meet these needs. The isotope program has a special responsibility to ensure a trained workforce in the production, purification and distribution of isotopes.

6. **We recommend that a robust investment be made into the education and training of personnel with expertise to develop new methods in the production, purification, and distribution of stable and radio-active isotopes.**

All of the issues and recommendations considered here will be important input for answering the 2nd NSACI charge in developing a long range plan for the Nuclear Isotopes Production and Application Program.

Introduction

The Fiscal Year (FY) 2009 President's Request Budget proposed to transfer the Isotope Production Program from the Department of Energy (DOE) Office of Nuclear Energy to the Office of Science's Office of Nuclear Physics, and rename it the National Isotope Production and Applications Program (NIPA). The transfer is in effect since the signing of the 2009 appropriations bill and there is a new name for the program, mainly, the Isotope Development and Production for Research and Applications. For the sake of consistency with the NSAC charge, we use NIPA for the remainder of this report.

In preparation for this transfer from NE to NP, the Nuclear Science Advisory Committee (NSAC) was requested to establish a standing subcommittee, the NSAC Isotope (NSACI) subcommittee, to advise the DOE Office of Nuclear Physics on specific questions concerning the National Isotope Production and Applications (NIPA) Program. NSAC received two charges from the DOE Office of Nuclear Physics. A copy of the full charge letter is attached as Appendix 1.

Charge 1:

As part of the NIPA Program, the FY 2009 President's Request includes $3,090,000 for the technical development and production of critical isotopes needed by the broad U.S. community for research purposes. NSACI is requested to consider broad community input regarding how research isotopes are used and to identify compelling research opportunities using isotopes. The subcommittee's response to this charge should include the identification and prioritization of the research opportunities; identification of the stable and radioactive isotopes that are needed to realize these opportunities, including estimated quantity and purity; technical options for producing each isotope; and the research and development efforts associated with the production of the isotope. Timely recommendations from NSACI will be important in order to initiate this program in FY 2009; for this reason an interim report is requested by January 31, 2009, and a final report by April 1, 2009.

This document is the final report for Charge 1.

Background

The Atoms for Peace program launched by President Eisenhower with an address to the United Nations National Assembly in 1953 and then followed by the Atomic Energy Act of 1954 has grown and translated into tremendous global advances in the 21st century. The infrastructure developed for making nuclear weapons was converted to the production of isotopes and made

available to the research infrastructure of the world. The scientific discoveries and advances made as a result of the availability of both stable and radioactive isotopes span widely from medicine to biology, physics, chemistry, and a broad range of applications in environmental and material sciences. Isotopes have also become crucial aspects of homeland security. They are utilized in new resource development, in energy from bio-fuels, in nuclear and petrochemical, drug discovery, health care therapies and diagnostics, nutrition, agriculture, and many others. In effect, the Atoms for Peace program led to the development of the modern field of nuclear medicine. The instrumentation of the gamma camera and Positron Emission Tomography (PET), as well as the most important radiopharmaceuticals, such ^{99m}Tc/^{99}Mo generator systems and many ^{99m}Tc radiopharmaceuticals including ^{99m}Tc sestamibi (a pharmaceutical agent used in nuclear medicine) for cardiac perfusion, ^{18}F flourodeoxyglucose (FDG), as well as ^{32}P, ^{198}Au, ^{131}I for therapy, were all developed with sole or partial support by DOE.

Isotopes were produced by the US Department of Energy for more than fifty years. In FY 2009, the President's Budget request included a proposal to move the Isotope Program currently in the Office of Nuclear Energy (NE) to the Office of Nuclear Physics (NP) within the Department's Office of Science. The goal of the Office of Nuclear Physics is to manage the Isotopes Program in an optimum fashion for the development and production of key isotopes for use in all the forefront areas of research in the sciences, in medicine, in industry, and national security. While the production of isotopes is centralized in the federal government, the variety of research supported by the use of DOE-produced isotopes span many agencies as varied as DOE Office of Science, NSF, National Institutes of Health, NNSA, EPA and NIST amongst others. There are also numerous industrial interests that use and produce isotopes for a variety of homeland security, research, and medical interests.

The office of Nuclear Physics organized a workshop August 5-7, 2008 in Rockville, MD bringing together all the varied stakeholders in the isotopes enterprise to discuss the development of a robust and prioritized program for isotope production. The report [1] of the "Workshop on the Nation's Needs for Isotopes: Present and Future" is now available on the web **(http://www.sc.doe.gov/henp/np/program/docs/Workshop%20Report_final.pdf)**. The workshop identified key isotopes from all the areas of research that were in short supply and highlighted several issues that are crucial to the future of the isotopes program.

- A reliable program in isotope production at DOE is crucial for the long term health of developments in medicine, basic physical and biological sciences, national security and industry.

- Many isotopes in domestic use are presently only produced by foreign suppliers, often a single or limited number of suppliers. This makes the isotope supply vulnerable to interruption or large price fluctuations beyond the control of the United States.

- Affordability is an important issue for research isotopes.

- The production capability of the NIPA program relies on facilities that are operated by DOE for other primary missions.

- There is a pressing need for more training and education programs in nuclear science and radiochemistry to provide the highly skilled work force for isotope application.

- The DOE Isotope Program and the resources that it has available to it today cannot fulfill the broad challenges and needs for current and future demands of the nation for isotopes.

The workshop by design did not address the relative priorities for uses for various isotopes. Setting priorities **between various disciplines and end users is clearly another major issue.**

Procedures:

The NSACI subcommittee membership was chosen to have broad representation from the research communities, industry, production, and homeland security. The list of NSACI members is given in Appendix 2. A special effort was made for the membership to have overlap with the many ongoing studies and the August Workshop. The studies of interest included the National Academies of Sciences (Institute of Medicine) study "*Isotopes for Medicine and Life Sciences*" published in 1995, the report on the 2008 meeting to discuss "*Existing and Future Radionuclide Requirements of the National Cancer Institute*", and the studies of the National Academies: "*Advancing Nuclear Medicine through Innovation*" published in2007 and "*Medical Isotope Production without Highly Enriched Uranium*" just published in 2009.

Three meetings were called by the subcommittee to address the first charge. The agendas for the meetings are attached in Appendix 3. The goal was to determine the landscape in isotope needs/uses/production, to determine needs for research isotopes across agencies, industry, and professional societies on the road to prioritization. The first meeting (Nov 13-14, 2008) was dedicated to hearing results of the several of the recent studies including the DOE workshop. The second meeting (Dec 15-16, 2008) was dedicated to hearing from the Office of

Management and Budget and the needs of the various federal agencies that fund research with isotopes. The third meeting (January 13-15, 2009) was dedicated to hearing about research needs from a wide range of professional societies and some of the facilities. Appendices 4 and 5 contain a listing of all agencies and professional societies that were contacted.

Overall, there is broad enthusiasm in favor of the Office of NP management and the potential opportunities presented to the isotope program. There is also an overwhelming concern for the education and training of students in radiochemistry, nuclear chemistry, and nuclear physics with the expertise required to make significant contributions toward the development of new and more traditional techniques using radioisotopes.

The NSACI committee divided the discussion of research opportunities into three areas: 1) medicine, pharmaceuticals, and biology, 2) physical sciences and engineering, and 3) national security and other applications. In each area, compelling research opportunities were considered and the subcommittee as a whole determined the priority research opportunities and recommendations. In order to realize the opportunities presented in each of these areas, isotope production capabilities will be of paramount importance. In the next chapter, we examine the present landscape for isotope production in the US.

Chapter 2: Landscape of Isotope Production in North America as of 2009

The landscape of isotope production in the US spans across many horizons and includes government, private industry, and research facilities at Universities. This chapter is divided into the following sections:

- Stable Isotopes
- Radionuclides produced in reactors
- Accelerator produced radionuclides which are further divided into sections reflecting the commercial suppliers, DOE labs and University/Hospital based producers.

By the nature of this enterprise there are, in many cases, overlaps of production sectors in supplying a particular isotope or radionuclide.

Stable Isotopes (Private and Government operated)

Active production of stable isotopes in the United States is primarily performed by the private sector with the exception of Helium-3 which is produced at the Savannah River facility operated by the DOE as a by-product of tritium decay. For the purposes of this report *production* refers

to a process whereby a stable isotope of an element is both separated and enriched to a useable level which is typically above 90 atom%.

The methods of isotope separation and enrichment employed by the private sector companies are distillation, chemical exchange, and thermal diffusion. The private companies which have these capabilities are Cambridge Isotope Laboratories, Eagle Pitcher, Isotec (Sigma Aldrich), and Spectra Gases. They produce the isotopes of carbon (13), oxygen (17, 18), and boron (10, 11) with capacity in the metric ton range and they offer a wide variety of compounds labeled with these isotopes. Supply is not an issue for any of these particular isotopes. Additionally, Isotec has a set of thermal diffusion columns which can be used for production of gaseous isotopes. These systems are not competitive in cost of production to those using the cryogenic centrifuges employed by foreign manufactures but do provide some domestic capability for some isotopes such as krypton, and xenon. Additionally, Spectra Gases has systems capable of enriching nitrogen (15), but the demand for this isotope is currently met by foreign entities at extremely reasonable prices.

Plasma isotope separation is a tool that has been used successfully in the United States weapons programs and is capable of producing specific isotopes at medium enrichments. These systems have been dismantled and are no longer available; however the technology is useful to an enrichment program if integrated with electromagnetic separators. A private company, Nonlinear Ion Dynamics (NID), LLC, in California has a plasma isotope enrichment system and has operated under an SBIR grant and private funding.

Research in the United States that uses stable and enriched isotopes is strategically important and in the Nation's interest. Therefore, the domestic capability for the production of these stable isotopes is strategically important to the United States in order to assure the continuation of research activities.

There are 339 naturally occurring isotopes (nuclides) on earth, and 250 of these are stable isotopes. The vast majority of the 250 naturally occurring stable isotopes are primarily made up of alkalis, alkali-earth, and metal stable isotopes and require the use of electromagnetic separators which are no longer in use within the United States.

The 220 stable non-gaseous isotopes are not currently produced in the United States. The reasons for this are several but include:

1. Most are only used in research applications in very limited quantities which will not attract private sector investment to manufacture them.

2. Most require separation and enrichment by means of either electromagnetic or gas centrifuge separators, and these systems are not operational in the United States and are prohibitively expensive to make and may require classified technology to build them and DOE security systems to manage them.
3. Many of the isotopes produced by electromagnetic separators are currently inventoried at ORNL in sufficient quantities to support limited research, however a number of isotopes (see Table 1) are no longer in inventory and/or are well below levels to sustain research even in the short term.
4. Foreign supply of the stable isotopes requiring centrifuges is currently meeting demand in most cases. However in a few instances the foreign supply is not meeting demand, e.g. ^{136}Xe, and ^{76}Ge.
5. The thermal diffusion method used for the separation and enrichment of the rare gas isotopes of argon, neon, krypton, and xenon is an expensive method of production.
6. Plasma isotope separators require more research to be used as a production tool.
7. Laser Isotope Separators appear prohibitively expensive to operate and currently limited in their scope of production for stable isotopes.

The alkalis, alkali-earth, and metal stable isotopes are essential to current research in health care and nutrition studies, which manipulate biochemistry at the cellular and sub-cellular level to prevent disease, as well as to offer personalized detection and treatment. The research cannot be done without the assurance of an ongoing supply of these isotopes. Some of these, identified in Table 1 from the August workshop, are already in short supply or no longer available and the only demonstrated method of production and separation for these stable isotopes is electromagnetic separators like the original Calutrons currently on standby at Oak Ridge National Laboratory. These systems have not operated due to the high cost of operations at ORNL and the 1990's implementation of the policy to have full cost recovery for all production at this facility. The income from the sale of the existing stockpiles of isotopes has not been sufficient to fund operation of the separators.

An important issue for stable isotope production is the potential use of these technologies for weapons of mass destruction. As such, much of the forefront work in this area may be classified and the technology is subject to security and export controls.

Table 1: Stable Isotopes of limited supply identified at the August Workshop.[1]

Isotope	Years remaining in inventory
^{157}Gd, Second Pass	0
^{204}Pb, Second Pass`	0
^{207}Pb, Second Pass	0
^{96}Ru	0
^{150}Sm, Second Pass	0
^{181}Ta	0
^{180}W, Second Pass	0
^{51}V	0
^{157}Gd	0.2
^{154}Gd, Second Pass	2.5
^{69}Ga	3.7
^{62}Ni	3.9

Reactor Production of Radionuclides

Worldwide, 278 research reactors are known to be operating in 56 countries supporting a variety of test, training, and research missions including isotope production. Eight new research reactors are under construction and eight more are currently being planned, all of them outside the U.S. The majority of these reactors are over 30 years old and the number of shutdown or decommissioned research reactors is about 487, by far more than are operating today. In the United States, there are currently 32 operating research reactors that are licensed by the U.S. Nuclear Regulatory Commission (NRC) and two reactors operated by the U.S. Department of Energy (DOE) for research and isotope production. Of these reactors, twenty-seven are owned and operated by universities and colleges for education and research purposes. Most of the U.S. research reactors are over 40 years old; however, many have recently completed or are currently in the process of re-licensing for an additional 20 years. A listing of U.S. research reactors having a thermal power of 1 MW or more is included in Table 2.

Table 2: U.S. Research Reactors ($\geq$ 1 MW_{th})

Research Reactor Facility	Power Level (MW)
Advanced Test Reactor (ATR)	250
High Flux Isotope Reactor (HFIR)	85
National Institute for Standards and Technology-NBSR	20
University of Missouri-Columbia	10
Massachusetts Institute of Technology	5
University of California-Davis	2.3
Rhode Island Nuclear Science Center	2
Washington State University	1.3
Kansas State University	1.25
Oregon State University	1.1
Penn State University	1.1
University of Texas at Austin	1.1
North Carolina State University	1
Texas A&M University	1
University of Massachusetts-Lowell	1
University of Wisconsin-Madison	1
U.S. Geological Survey	1
Armed Forces Radiobiology Research Institute	1

The number of DOE research reactors has decreased since 1980, primarily due to aging infrastructure and a change in programmatic focus by the DOE in the 1980s. Likewise, the number of university research reactors (URR) in the U.S. has decreased by over 50% since 1980. This trend was partially due to the closure of many nuclear engineering programs following a contraction of the nuclear industry, but was also caused by the lack of funding necessary to

replace failed or obsolete research and reactor control instrumentation. Nearly all URR facilities had, and still have, very limited funding to upgrade existing systems. The age of the URR instrumentation and control systems impacted their reliability and availability and thus limited the number of users. In 1998, the DOE Office of Nuclear Energy (DOE-NE) acted to support the URR facilities and created the University Reactor Instrumentation grants to replace reactor control and safety system equipment at the aging URR facilities. This program and other funding programs provided targeted support to the URR community and appeared to halt the trend of URR closures. Unfortunately, these programs were cancelled in 2006. There are no current plans for replacement funding programs, which again places many URR facilities at risk of closure.

Isotope Production in U.S. Research Reactors

The University of Missouri reactor (MURR) may be considered unique among U.S. research reactors because a large percentage of its operations are solely dedicated to the large scale production of medical radioisotopes. MURR operates on a regular 6.5 day/week operating schedule and has availability of approximately 90% during its scheduled operating time. This schedule and high availability make it ideal for routine, reliable production and shipment of radioisotopes. In 2007, MURR produced and shipped over 30,000 Ci of ^{153}Sm, ^{90}Y, ^{33}P, ^{32}P, ^{166}Ho, and ^{177}Lu for medical research, clinical trials, and commercial applications. MURR is also actively engaged with industry to become a reliable domestic source of ^{99}Mo for the production of ^{99m}Tc generators used in approximately 85% of all nuclear medicine procedures. ^{99}Mo is currently imported from Canada and Europe.

The smaller research reactors also provide important radioisotopes to researchers and commercial radiotracer companies. These users have a need for small batch quantities of relatively short-lived radioisotopes that would not be obtainable or useful if provided by a reactor facility located hundreds of miles away. Examples of some of these short-live isotopes (<100 days) are provided in Table 3.

These radioisotopes do not have a substantial “shelf-life” and require just-in-time production and delivery. The smaller research reactors have flexible staff, facilities and operational schedules to provide this capability. The distribution of these small research reactors throughout the U.S. ensures that customers in all regions can be supplied with the short-lived radioisotopes to support their needs.

Use of the DOE research reactors for the production of radioisotopes is somewhat limited by a policy adopted in 1965 that the U.S. government is to refrain from competing with private

sources when the materials are reasonably available commercially. However, these reactors may and do engage in the production of isotopes that can only be produced in the high flux available in their cores or that are being developed for future commercialization. At a consequence of their multiple missions, in some cases, the primary mission at the reactor leads to operating schedules that are not well matched for optimum isotope production. Examples of radioisotopes that can be produced at the DOE reactors are provided in Table 4.

Table 3: Short-lived radioisotopes produced at small research reactors (≤5MW).

Isotope	Half-life	Application
^{24}Na	15.0 hr	Tracer, Marker
^{28}Al	2.25 m	Student Laboratory
^{41}Ar	1.82 hr	Tracer
^{46}Sc	83.8 d	Tracer
^{76}As	26.3 h	Cancer therapy
^{79}Kr	1.4 d	Gas Tracer
^{82}Br	1.47 d	Tracer
^{90}Y	2.7 d	Cancer therapy
^{124}Sb	60.2 d	Tracer
^{133}Xe	5.24 d	Tracer, NPT Monitors
^{135}Xe	9.1 hr	NPT Monitors
^{140}La	1.68 d	Tracer, Gamma Source
^{192}Ir	73.8 d	Tracer
^{198}Au	2.3 d	Cancer therapy, marker

Table 4: Radioisotopes which can be produced at DOE research reactors.

Isotope	Application
^{252}Cf	Neutron source – multiple uses
^{63}Ni	Pure beta source
^{238}Pu	Power source
^{60}Co	High specific-activity gamma source
^{177}Lu	Clinical trials
^{166}Ho/^{166}Dy	Targeted therapy, Ablation
^{166m}Ho	Calibration source
^{125m}Te	Diagnostic imaging
^{228,229}Th	Targeted therapy, Alpha emitter
^{227}Ac	Targeted therapy, Alpha emitter
^{99}Mo	Diagnostic imaging-Backup production only
^{64}Cu	Diagnostic imaging, Therapy
^{131}Ba/^{131}Ce	Cancer Brachytherapy
^{103}Ru/^{103m}Rh	Targeted therapy
^{186}Re	Targeted therapy
^{147}Pm	Power source
^{210}Po	Power source
^{170}Tm	Power source
^{171}Tm	Power source
^{242}Cm	Power source
^{35}S	Power source
^{144}Ce	Power source
^{75}Se	Well logging
^{225}Ac	Targeted Therapy, Alpha Emitter

It should be pointed out that some of these radionuclides that are produced via the (n,γ) reaction will have limited utility because of the low specific activity associated with this approach to production (e.g. ^{186}Re, ^{64}Cu).

The heavy actinides, such as ^{252}Cf, can be produced only at HFIR. This capability is unique in the western world with Russia being the only other potential supplier of these isotopes. The HFIR is primarily dedicated to the neutron scattering sciences mission of the DOE Office of Science, but is able to produce these heavy isotopes while also satisfying its neutron scattering mission.

In summary, the number of research reactors available to produce radioisotopes worldwide is diminishing and those that remain are aging. There seems to be activity abroad to build new research reactors to fill future needs. However, the US fleet of aging research reactors remains constant for the time being. The U.S. URRs are in need of resources to refurbish and re-license. Only one reactor, MURR, is positioned to supply the medical and commercial needs of the country on a routine basis. The smaller URRs are currently able to meet the regional needs for short half-life isotopes for the time being, but the country cannot afford to lose many of these valuable resources. The DOE reactors are currently able to produce the unique high specific-activity isotopes and heavy actinides demands of the U.S., however, should the operation of the DOE reactors be interrupted, the only alternative source is Russia.

Accelerator Production of Radionuclides

Background

Accelerator isotopes are neutron deficient and are produced in either cyclotrons or linear accelerators by proton, deuteron, or alpha particle bombardment. Accelerator isotope applications generally complement reactor isotope applications, and accelerator isotopes usually decay by β, γ or positron emission or electron capture. Accelerator beam parameters, especially beam energy and beam current, are important considerations in the production of isotopes. Beam energy determines what isotopes are produced (and by what nuclear reaction) and beam current determines how much is produced. Low energy cyclotrons (<30 MeV) are generally used to produce short-lived isotopes (^{11}C, ^{15}N, and ^{18}F) that are used in clinical positron emission tomography (PET) and PET R&D. However, many other isotopes can be made at lower energies). Several commercial isotopes are produced in 30 MeV cyclotrons operated by industrial isotope producers and radiopharmaceutical manufacturers, e.g. ^{111}In, ^{201}Tl, ^{67}Ga,

^{123}I and ^{103}Pd. Higher energy accelerators are usually operated by government laboratories and make products that require higher energy, e.g. ^{82}Sr.

Commercial Sources

Several commercial companies currently operate low and medium energy accelerators in the U.S. Many of these companies produce radioisotopes only for their own use. Other commercial companies sell the radioisotopes they produce to others. There are also many PET cyclotrons that are operated by joint ventures or partnerships with universities or hospitals. In many cases the hospital or university produces their own PET radiopharmaceuticals while the commercial partner markets any excess PET radiopharmaceutical capacity to other facilities. A number of these commercial capabilities are discussed below. Table 5 lists the commercial radiopharmacies (CRP) and PET cyclotrons in the US. (Note corporate ownership of these commercial entities has changed rapidly recently. The corporate structure and name identified may not be completely up to date.)

Table 5: Commercial Radiopharmacies (CRP) and PET cyclotrons in the US.

Company	CRP	PET Cyclotrons
Cardinal Health NPS	182	20
Covidien	36	1
GE Healthcare	31	2
IBA Molecular	11	11
PETNET	42	42
Triad	28	7
Independent	96	23
Institutional[1]	69	6
Totals	**495**	**112[2]**

1. The number of institutional PET cyclotrons that operate as CRPs.
2. The total number of cyclotrons includes the 60 PET cyclotrons that are licensed as pharmacies are included in the total.

Lantheus Medical Imaging

In their North Billerica, MA facility Lantheus operates several medium energy cyclotrons. They produce ^{201}Tl and ^{67}Ga for use in their FDA-approved radiopharmaceuticals. Lantheus is largely self-sufficient for these radioisotopes and only relies on outside source of supply if there are operational issues with the cyclotrons such as an extended outage or un-scheduled maintenance. Many of the other commercial radiopharmaceutical companies have made these radioisotopes available to each other if one of them has significant operational problems with their cyclotrons. This informal back up arrangement has worked well for many years. Lantheus does not routinely sell these radioisotopes in the open market.

Covidien

Covidien operates several medium energy cyclotrons at their facility in Maryland Heights, MO. They routinely produce ^{201}Tl, ^{123}I, ^{111}In, and ^{67}Ga for use in their FDA-approved radiopharmaceuticals. On occasion they have also provided backup supply of these radioisotopes to the other radiopharmaceutical manufacturers. Covidien also operates more than 35 nuclear pharmacies. At a number of these nuclear pharmacies Covidien has partnered with a university or hospital to jointly produce ^{18}F FDG using low energy PET cyclotrons. This FDG is marketed to facilities located within a strategic distance to the nuclear pharmacy taking into account the short half-life of ^{18}F.

MDS Nordion

MDS Nordion's Vancouver Operation has 3 cyclotrons (two high current TR30 cyclotrons, 30 MeV, and a single CP42 cyclotron, 42 MeV) that produce the standard commercially available radionuclides on a routine basis (^{201}Tl, ^{123}I, ^{67}Ga, ^{111}In, ^{103}Pd) as well as smaller amounts of ^{64}Cu for research centers. As with the other commercial vendors Nordion supplies other vendors during outages across the cyclotron sites.

GE Healthcare

GE Healthcare currently operates several medium energy accelerators in their Arlington Heights, IL and S. Plainfield, NJ facilities. They manufacture ^{201}Tl, ^{123}I, and ^{111}In in these cyclotrons for use in their own FDA-approved radiopharmaceuticals. As with Covidien and Lantheus they do not routinely sell these radioisotopes commercially but have in the past served to provide backup supply top the other two major radiopharmaceutical manufacturers. GE healthcare also operates more than 30 nuclear pharmacies.

PETNET

PETNET, a Division of Siemens currently operates 42 PET cyclotrons in the U.S. They market ^{18}F FDG, ^{13}N NH_4, and provide some ^{11}C labeled compounds.

Cardinal Health

Cardinal Health currently operates nearly 182 nuclear pharmacies in the U.S. Twenty of these facilities are co-located with a PET cyclotron and are producing ^{18}F FDG.

IBA Molecular

IBA Molecular currently operates eleven PET cyclotrons throughout the Eastern U.S. These cyclotrons are used primarily for the production of ^{18}F FDG.

Independent Nuclear Pharmacies

There are more than 96 independent nuclear pharmacies located in the U.S. Some of these operate low energy cyclotrons for the production of ^{18}F FDG.

Trace Life Sciences/NuView

NuView in Denton, TX has two medium energy cyclotrons. They also have a 70 MeV LINAC which has been used at lower energy (33 MeV) to produce several medical radioisotopes. Trace has routinely operated four of the six target stations on the LINAC. The CP-42 has been operating for several years but the CS-30, which was relocated from Mount Sinai Medical Center has not been fully commissioned yet. The LINAC has been producing ^{201}Tl, ^{67}Cu, ^{64}Cu, ^{111}In, and ^{123}I for commercial distribution. Trace has submitted Drug Master Files (DMF) to the FDA for all of these products. They also have an aNDA for the production of Thallous Chloride, which has been distributed through NuView. Trace commercially distributes these radioisotopes for commercial use and for research and clinical studies.

DOE Capabilities

The discussion below focuses on the Department of Energy production capabilities on high energy accelerators at Brookhaven National Laboratory, Los Alamos National Laboratory, and international accelerator collaborators. Examples of isotopes produced at these facilities are given in Table 6.

Brookhaven National Laboratory Specific Capabilities

This program is part of the Medical Department at Brookhaven National Laboratory. It uses the **Brookhaven Linac Isotope Producer (BLIP),** and the associated **Medical Department laboratory and hot cell complex** to develop, prepare, and distribute to the nuclear medicine community and industry some radioisotopes that are difficult to produce or not available elsewhere. BLIP, built in 1972, was the world's first facility to utilize high energy protons for radioisotope production by diverting the excess beam of the 200 MeV proton LINAC to special targets. After several upgrades BLIP remains a world class facility and continues to serve as an international resource for the production of many isotopes crucial to nuclear medicine and generally unavailable elsewhere. The overall effort entails: (1) target design, fabrication and testing; (2) irradiations; (3) radiochemical processing by remote methods in the 9 hot cells of the Target Processing Lab; (4) quality control and analysis; (5) waste disposal; (6) facility maintenance; (7) new isotope and application development; and (8)customer liaison, marketing, packaging, and shipping. Service irradiations (without chemistry) are also performed.

Los Alamos National Laboratory Specific Capabilities

The **Los Alamos Neutron Science Center** is the cornerstone of Los Alamos isotope production. Historically, targets were irradiated at the beam stop at LANSCE from the inception of the facility in the 1970s. Irradiation of these targets with 800 MeV H+ protons produced isotopes by a nuclear process known as spallation. It became evident in the mid-1990's that continued delivery of H+ proton beam to the beam stop area would cease because of a lack of programmatic requirements. The Isotope Program proposed the construction of a new target irradiation facility that would divert beam from the existing H+ beam line in the transition region from the drift tube linac (DTL) to the side-coupled cavity linac (SCCL) into a new beam line and target station housed in a new facility adjacent to the existing accelerator facility. The energy of the protons in this transition region is 100 MeV, and production of isotopes in targets irradiated in this facility occur primarily by (p,xn) nuclear reactions. Approval was received for this proposal and the construction project was initiated in FY 1999. This new construction project, funded by DOE-NE, was completed in FY 2003 at a cost of $23.5 M. The 100 MeV Isotope Production Facility (IPF) has operated since the spring of 2004, and irradiates targets while LANSCE is operating for other experimental science programs. The 100 MeV IPF has also operated in a dedicated mode when target irradiations from other facilities are not available.

The irradiated targets are transported from LANSCE in a shielded transportation container. The **TA-48 Hot Cell facility** at the Main Radiochemistry Site, Building RC-1 is the primary hot cell facility for accelerator isotope production. It consists of two banks of 6 chemical processing

cells connected at one end by a large multipurpose "dispensary" cell, where all materials are received into and from which all materials leave the facility. Supporting facilities including several radiochemistry laboratories, a machine shop, two analytical laboratories, an extensive counting room facility, and offices for personnel surrounds the hot cell facility. This facility, along with the Laboratory's waste handling facilities, is absolutely essential for conducting the LANSCE isotope production mission.

Table 6: Examples of radioisotopes produced with DOE accelerators and isotope applications.

- **Positron Emission Tomography (PET)**
  - $^{82}Sr/^{82}Rb$ – myocardial imaging
  - $^{68}Ge/^{68}Ga$ – calibration sources for PET scanners, radiopharmaceutical research
  - $^{72}Se/^{72}As$ – oncological radiopharmaceuticals
- **Isotopes for cancer therapy**
  - ^{67}Cu – treatment of non-Hodgkin's Lymphoma
  - ^{103}Pd – seed implants for prostate cancer treatment
  - ^{76}As – bone pain palliation, radiopharmaceutical research for cancer treatment
- **Environmental and research radiotracers**
  - ^{32}Si – biological oceanography, global climate
  - ^{26}Al – acid rain, Alzheimer's research, materials
  - ^{95m}Tc – technetium behavior in ecosystems

University Based Production of Radionuclides

The university/hospital based accelerators are typically cyclotrons with proton energies below 20 MeV and are focused on internal programs for the production of the positron emitting isotopes such as ^{11}C, ^{15}O, and ^{18}F.

There are two principle suppliers of radionuclides for research in the university system: Washington University (St. Louis) School of Medicine and the University of Wisconsin. The University of Wisconsin program is fairly modest in scope but does provide ^{64}Cu to several research groups in the U.S. The University of Buffalo operates a Cyclone-30 which has produced ^{18}F, ^{13}N, ^{11}C, ^{111}In, ^{62}Cu, ^{124}I and ^{15}O. Although they have a separate beam line and vault for target irradiation, they do not have hot cells capable of producing large quantities of radioisotopes. They are capable of producing quantities up to 1 Ci of ^{111}In per week, and had plans to submit a Drug Master File by the close of 2008. They have also produced batches of 110 mCi of ^{124}I per target.

The Washington University program has been supported for five years by the National Cancer Institute as a Research Resource to support Cancer researchers within the NCI system as well as other researchers needing radionuclides not readily available through commercial routes. This program has been extremely successful in providing ^{64}Cu as well as other radionuclides such as ^{76}Br, ^{86}Y, ^{94m}Tc, ^{66}Ga. The supply of radionuclides is based on two small cyclotrons, a CS-15 and a JSW, both accelerating 15 MeV protons. One of the mandates for this program was to transfer the technologies gained through this experience to a commercial partner. Washington University is in the process of doing this as of early 2009.

The Washington University experience illustrates that a small program can be effective if supported and that the program has a focus. This experience can serve as a model for other programs in support of radionuclide supplies.

There are more than 110 low and medium energy cyclotrons being operated in the U.S. largely for the production of ^{18}F FDG. Most of these cyclotrons are dramatically underutilized with less than 25% duty cycle. If one adds in the more heavily used commercial cyclotrons there are a total of close to 125 cyclotrons that have spare capacity and could be utilized for more production of research and commercialized radioisotopes.

Chapter 3: Research Opportunities in Biology, Medicine, and Pharmaceuticals

The majority of the isotopic material used in medical and biological research is used to support clinical trials. That said, there is still a significant demand for radioisotopes for use in research during radiochemical, in vitro, and in vivo preclinical investigations. These investigations are critical in the development of radiopharmaceuticals for diagnostic and therapeutic applications.

At the very earliest stage of development, a radionuclide is used to test labeling techniques that are used to radiolabel a targeting molecule. Obviously, given the cost of the starting material, the need to maximize the yield of the reaction is paramount. This is also important in maximizing the specific activity of the compound in question. In many cases, there is a limited number of sites on the target cell. In order to maximize the signal to noise ratio, or to maximize the therapeutic effect, it is important to have the greatest number of radioactive atoms attached to the target. These investigations are often limited to synthesis and analysis using standard techniques such as chromatography.

Once these investigations have been completed, testing of the biologic activity would be undertaken by utilizing cells that express the target that are exposed to the

radiopharmaceutical. Usually, specific binding is determined by utilizing a control cell line of similar characteristics save the target itself and adding a substantial excess of the unlabeled targeting molecule to block specific binding to the target. In the case of a therapeutic conjugate, cell survival assays would also be undertaken to assess the cytotoxicity of the conjugate.

Once a radiopharmaceutical has passed these tests, testing in vivo will be done to assess the compounds ability to target the site of interest. In the case of human tumors, an animal with a compromised immune system will be used so that a xenograft of a tumor of interest can be grown. Usually, administration of the radiopharmaceutical will be via the vein as is the case in the nuclear medicine clinic. In the majority of cases, a combination of imaging of the radiopharmaceutical will be combined with post mortem tissue counting to determine relative and absolute uptake of the material.

Radioactivity can be selectively administered into patients by direct injection and if the radiation is in the right form, can selectively target human tumors and if sufficiently concentrated can destroy the tumors, without excessive damage to normal tissues. The prototype for this approach was introduced in the early 1940s, as radioactive iodine, in the form of ^{131}I which could target human thyroid cancer and in some cases cure patients of metastatic tumors which would have otherwise been fatal. Shortly after this, ^{32}P was introduced for targeting of human bone marrow disorders and was an early and quite effective therapy for abnormal states of myelodysplasia (pre-leukemia disorders) including polycythemia vera (abnormal increase in blood cells (primarily red blood cells) due to excess production of the cells by the bone marrow). These radionuclides were generally introduced in common chemical forms into the body, ^{32}P in phosphate form or ^{131}I as sodium iodide and because of natural processes within proliferating tissues achieve therapeutic concentrations. Although ^{32}P has been supplanted by more selective chemotherapies, ^{131}I continues to be the front-line drug for therapy of advanced thyroid cancer.

The practice of using radioactivity which is introduced into the patient by injection of relatively simple chemical forms continues to this day. For example Holmium and Dysprosium are injected into the joint space of patients for selective therapy of arthritis; ^{153}Sm, ^{89}Sr as simple chelates take advantage of the natural bone seeking properties of this class of chemical element. These two drugs have been approved by the Food and Drug Administration. Bone seeking elements that have slightly improved quality for palliative therapy are also being explored in clinical trials. These include ^{224}Ra and ^{110}Sn. Both are given as a simple salt, introduced in the patients with metastatic prostate cancer and are effective aviation therapies.

Targeted therapies with radio peptides or radio labeled antibodies have been introduced. Patients with non-Hodgkin's lymphoma are now routinely treated, especially in the late stage of their disease, with radio immunotherapy. This form of modern targeted therapies in medicine takes advantage of knowledge of the biology of cancer, and the specific biomolecules that are important in causing or maintaining the neoplastic state (abnormal proliferation of cells). In this case, an antibody or protein is used which is the carrier for the radioactivity, but so confers a specific binding property to a known component of any class of tumors: for example the radiolabeled peptide ^{90}Y (Yttrium DOTATOC) selectively binds to an endocrine receptor on carcinoid tumors, somatostatin type II (growth hormone inhibiting hormone). The targeting occurs much like a key (the radiopeptide) fitting into a lock (the somatostatin receptor), and over time sufficient radioactivity is deposited in the region of the tumor to damage the proliferating capacity of the tumor, in some cases eradicating sites of the tumor completely. In many instances clinical benefit is obtained from the use of the radioactivity, and especially in patients with advanced disease.

The use of therapeutic radionuclides is expanding in clinical research, and over the course of five years, it is likely that several additional FDA approved clinical applications will become best practice for specific clinical indications.

In general, it is in the particulate form of the radiation which is most likely to be useful for the purpose of depositing localized radiation in sufficient quantities to kill tumors without damaging normal tissues. Therapeutic radioisotopes are chosen for their radiation properties, including type of particulate radiation emitted, half-life, and energy. Radionuclides that are proposed for this type of therapeutic radiation usually emit one of three types of radiation: Auger electrons, beta particles, or alpha particles.

Auger electrons are emitted during the process of electron capture decay, and have the property of depositing energy very densely during the track of their decay. This process is referred to as high linear energy transfer (LET) of radiation to tissues. Obviously this process would be highly advantageous if a radionuclide were targeted to a tumor because then that energy would be deposited within and maximally damaging the tumor, sparing surrounding normal tissues. Beta particles are emitted from relatively neutron rich radionuclides that in general are produced in reactors as part of fission processes. The nuclear decay leads to the simultaneous emission of a neutrino, and a beta particle with a sharing of the available energy so that a description of the population of beta particles emitted has a distribution of decays for a given radionuclide characterized by more than simply the median and maximum energy. This is important for radiotherapy because the distance that a particle travels through tissue is proportional to its emission energy. Medium energy beta particles such as those from ^{131}I have

a path length which is up to about 300 μ in tissues, while higher energy betas from radionuclides such as ^{90}Y have path lengths that may range up to 1 cm in tissue. This distribution of energies is considered undesirable because a significant portion of the deposited energy, especially for small tumors, will be deposited outside the tumor and in normal tissues. Alpha particles on the other hand are emitted with discrete energies, and because of their higher energy, slower velocities and higher charges deposit a large amount of energy along a relatively short track in tissues. It is generally considered that the cell nucleus is the killing zone within a cancer cell, and alpha particles traversing through a cell nucleus will deposit enough energy to kill the cell.

Different forms of radiation are useful for targeted therapy depending on the specifics of localization within a tumor or mass. For very small microscopic tumors, beta particles are less desirable because much of their energy would be deposited outside the tumor mass. On the other hand, if radionuclides bearing alpha particles could be targeted to cancer cells, it would take only a few radioactive decays to kill the cell.

As targeted vehicles including antibodies and peptides become more and more selective for selective binding to biomolecules attached to cancer cells, radionuclides which emit alpha particles have become more and more desirable. These radionuclides have been relatively difficult to get in sufficient quantities. The short-lived alpha emitters are particularly in demand, especially ^{225}Ac, ^{213}Bi, and ^{211}At.

Another area of compelling research with isotopes is in the development of pairs of isotopes in radiopharmaceuticals that can be used simultaneously for therapy and dosimetry. The therapeutic part of this research tests the ability of the radiation to either effectively ablate the tumor as determined by physical measurements or to “cure” the tumor. In order to better gauge the window of effectiveness and toxicity for the therapeutic agent, a surrogate agent is used. The second part of these new developments is the determination of the dosimetry of the compound. This information is then used to determine the dose that would be received by the target tumor and normal tissue without using the therapeutic agent itself. Obviously, the best option would be to use an isotope of the same element so that the chemical issues are the same. In Table 7, we present several examples of such therapeutic/dosimetry pairs.

Table 7: Pairs of isotopes that can be simultaneously used for dosimetry and therapy.

Therapy mechanism	Therapeutic radionuclide	Diagnostic radionuclide for dosimetry	Decay mode of dosimetry agent
Beta decay	^{67}Cu	^{64}Cu	Positron
Beta decay	^{90}Y	^{86}Y	Positron
Beta decay	^{131}I	^{124}I	Positron
Alpha decay (daughter)	^{212}Pb (^{212}Bi)	^{203}Pb	Single Photon

For those compounds that pass these hurdles, patient studies will be undertaken either under the watch of a radioactive drug research committee and the institutional review board or after the investigators have applied to the Food and Drug Administration (FDA) for an Investigational New Drug (IND) status for the compound.

It should be evident that the amount of radionuclide required at each stage of development increases substantially. Thus, in parallel to the biomedical investigations underway, there needs to be a parallel effort to increase the amount of the radionuclide produced to support the research effort.

Identification of the stable and radioactive isotopes that are needed to realize these opportunities

Stable Isotopes:
Virtually all research studies of human *in vivo* metabolism today, in adults as well as children, employ stable rather than radioactive tracers. The movement away from radiotracers for such studies came over the last 35 years in large part due to the continued availability of stable isotopes from production programs at Los Alamos and Oak Ridge National Laboratories. The widespread use of ^{2}H, ^{13}C, and ^{18}O throughout basic and clinical biochemical research has made commercial production of these isotopes feasible and industry sources are readily available. ^{15}N demand is also met currently by industry sources, but it is not available domestically and there is no domestic generator of a new inventory. The latter is, potentially, no trivial problem because nitrogen is an indispensible dietary nutrient, especially in its role as the essential

nutrient in amino acids, the building blocks of proteins. Thus, since there is no long-lived radiotracer alternative, an absence of ^{15}N would curtail essentially all human studies of nitrogen metabolism. F, Na, Mg, P, S, Cl, K, Ca, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Mo and I are essential nutrients in man. Some of these elements (e.g., F, Na, P, Mn, I) are mono-isotopic and, thus, not amenable for use in tracer studies. The remainder, however, have stable nuclides that are critically necessary for investigation of the requirements and metabolism of these indispensible nutrients in humans and animals.[2,3,4] Although these isotopes exist in current DOE inventory, the great bulk of the stable mineral isotopes used for human research are supplied by Russia and there is great concern for future availability. This concern has been expressed previously.[5] It is not an exaggeration to say that research and clinical studies of essential mineral nutrient metabolism in man will come to a complete halt if the supply of these elements is curtailed. These concerns are no less acute or impactful in the domains of studying aquatic and terrestrial ecosystems where, in addition to the nuclides discussed above, the supply of stable isotopes of B, Cd, Ba, Hg, and Pb are, likewise, vitally essential for research into the impact of our environment on biological systems.[4]

Radioactive isotopes

The radionuclide and the radiochemical purity of a given isotope of interest are critical. In the former instance, contaminating radionuclides can degrade the quality of the image, increase the dose to the patient, and render the product unusable according to the specifications for the radiopharmaceutical. In the latter instance, the chemical form of the material can potentially reduce the yield of the chemical reactions and potentially reduce the specific activity of the final product if a stable contaminant competes with the radionuclide during synthesis.

Estimated quantity and purity of isotopes of high priority for Biology, Medicine, and Pharmaceuticals

The opportunities identified in this area are listed in Table 8. The opportunities are listed in priority order for this section. Within each opportunity, if there is particular priority to one isotope, it is noted below. Most of these follow the recommendations of the "Report of Meeting Held to Discuss Existing and Future Radionuclide Requirements of the National Cancer Institute", held on April 30, 2008, the 2007 report of the National Research Council's Committee on the State of Nuclear Medicine, "Advancing Nuclear Medicine Through Innovation", and the list of projected isotope needs presented to the Committee by the National Cancer Institute from the on-going DOE-NIH working group.

Alpha therapies have extraordinary research potential and the isotopes of interest are ^{225}Ac, ^{211}At, and ^{212}Pb.The August isotope workshop identified the quantities of ^{225}Ac that would be needed for various stage clinical trails. One important factor for this isotope is that a potentially

important interim source of ^{225}Ac is to recover the ^{229}Th parent from stores of ^{233}U that are scheduled to be diluted and disposed of, a process that would make them unsuitable for this purpose. It is estimated that a factor of four more material is needed at this point and if a Phase II study is undertaken, an order of magnitude more material will be needed. Because rapid action may be needed here, and the linking of ^{225}Ac with another isotope with the same parent, ^{213}Bi, it is given the highest priority in this opportunity.

The ^{211}At is needed in similar amounts, a factor of four more material now and an order of magnitude more should a Phase II study be undertaken. The ^{212}Pb availability is easier to expand than those of ^{225}Ac and ^{211}At since the grandparent ^{232}U has a shorter half-life and can be produced by neutron irradiation of ^{231}Pa.

Several low energy accelerators located at separate facilities in the United States are currently producing key medical research isotopes (^{64}Cu, ^{124}I). Other medical research isotopes (^{86}Y, ^{203}Pb, ^{76}Br, ^{77}Br) could also be produced at these accelerators. However, since these are research radionuclides and a large commercial market has not been established yet, operators of these accelerators do not have a significant incentive to produce these routinely. As a result, these radionuclides are not always readily available. There are significant advantages foreseen for sharing radiochemistry techniques and targetry technologies across accelerators located around the country in producing these research isotopes. These four diagnostic agents paired with theuraputic agents can all be made at all of these existing low energy accelerators, but to ensure regular and long term availability, there is a need for increased networking of producers and R&D in order to increase quantities needed by researchers. Within this opportunity, priority is not given to any individual pair of isotopes.

A continuously growing need for ^{89}Zr was projected by the DOE-NIH joint working group. This isotope is also produced at lower energy facilities than DOE currently operates and increased and regular availability requires coordination of production and the sharing of production and chemistry techniques. The production of ^{67}Cu requires higher energy accelerators than are currently avaiable at three sites, two of which are DOE NIPA facilities. The high demand projected for the future could not be met with current capacities. An isotope for medical applications should be considered a research isotope until it has been given New Drug Approval (NDA) by the FDA. Preclinical and clinical research subjects are administered these materials under guidance of a radioactive drug research committee or Investigational New Drug status. Until that time, the isotope should be considered as a research material and not subject to petitioning from a private provider. The experience to date has shown that premature abandonment of production has resulted in unsupported increase in price and a spotty ability to meet the demand of the research community.

Table 8: Research opportunities in Medicine, Pharmaceuticals and Biology in order of relative priority

Research Activity	Isotope	Issue/Action
Alpha therapy	^{225}Ac ^{211}At ^{212}Pb	Current sources are limited. One valuable source for ^{225}Ac, extraction of ^{229}Th from ^{233}U may soon be lost.
Diagnostic dosimetry for proven therapeutic agents	^{64}Cu ^{86}Y ^{124}I ^{203}Pb	Used in conjunction with ^{67}Cu therapy ^{90}Y therapy ^{131}I therapy and immune-diagnosis ^{212}Pb therapy The issue is the need for a coordinated network of production facilities to provide broad availability. There is need for R&D for common target and chemical extraction procedures.
Diagnostic Tracer	^{89}Zr	Immune-diagnosis 3.27 d half-life allows longer temporal window for imaging of MoAbs, metabolism, bioincorporation, stemcell trafficking, etc.
Therapeutic	^{67}Cu	Requires specialized high energy production facilities and enriched targets

Chapter 4: Research Opportunities with isotopes in Physical Sciences and Engineering

Isotopes give unique responses under various excitations in solids, liquids, and gases. This is either due to the mass difference, which couples to electronic degrees of freedom, or nuclear structure, which shows large variations even with a single neutron addition. This unique behavior of isotopes lends itself to a plethora of useful applications. Thus, in almost all branches of sciences and engineering, from humanities to environmental science to nuclear physics and geology, isotopes have found fundamental and technological applications. For example, isotopes have changed the way we produce energy, develop industrial diagnostic methods, learn about our past in sociological (archeology), geological (terrestrial and extra-terrestrial), ecological (carbon and nitrogen cycle), and astronomical sense, help us secure our future energy needs, manage our natural resources like water and forests, and provide home and food safety. Therefore, many aspects of isotope production, use, detection, and education for research are relevant and worthy of continued support by DOE.

While the discovery of isotopes is less than 100 years old, today we are aware of about 250 stable isotopes of the 90 naturally occurring elements. The number of natural and artificial radioactive isotopes exceeds 3200, already, and this number keeps growing every year. F. Soddy's discovery (1910) of lead (Pb) obtained by decay of uranium and thorium differing in mass was considered a peculiarity of radioactive materials. In 1913 Soddy, and independently Fajan, developed a displacement law, which explains the change in mass and in the place in the periodic table after α-decay or β-decay takes place, and extended its implications on the formation of isotopes.

In this chapter, we highlight several research opportunities with isotopes across various fields. Isotopes are essential tools in basic research across all of *nuclear physics*. Many of the most important experiments at the frontiers depend on reliable and affordable availability of nuclear isotopes. In understanding the nucleon at the fundamental quark and gluon level, targets and beams of ^{2}H and ^{3}He allow access to the neutron. In looking beyond the Standard Model with tests of fundamental symmetries, the important experiments rely on a number of key isotopes. Finally, one of the central thrusts of modern nuclear physics is to understand the structure and properties of rare isotopes – those that exist only for a short time but which play a central role in the formation of the elements. A new user facility (FRIB) is planned in the U.S. to address this important area.

Basic principles, intrinsic characteristics, and fundamental applications of isotopes

In *nuclear physics***,** there are many uses of enriched isotopes, stable and radioactive. Enriched stable isotopes are needed for targets and for accelerated beams at various laboratories producing both stable and radioactive beams needed to study the structure of nuclei. For example, ^{48}Ca is a very neutron rich isotope that is commonly used as a beam at various nuclear physics laboratories to study the properties of exotic nuclei far from stability. Also, it is used in fragmentation reactions to produce very exotic radioactive beams. A future supply of stable highly enriched isotopes of many different elements is necessary for forefront experiments in nuclear physics. Below we list some examples of frontier research experiments with special needs in isotopes.

The Argonne Tandem Linac Accelerator System (ATLAS) is a DOE-funded national user facility for the investigation of the structure and reactions of atomic nuclei in the vicinity of the Coulomb barrier. A major advance in rare-isotope capabilities at ATLAS will be the *Californium Rare Ion Breeder Upgrade (CARIBU)***.** Rare isotopes will be obtained from a one-Curie ^{252}Cf (Californium) fission source located in a large gas catcher from which they will be extracted, mass separated, and transported to an Electron Cyclotron Resonance (ECR) source for charge breeding prior to acceleration in ATLAS. This will provide accelerated neutron-rich beams with intensities up to 7×10^5/s, and will offer unique capabilities for a few hundred isotopes, many of which cannot be extracted readily from Isotope Separator On Line (ISOL) type sources. In addition, it will make these accelerated beams available at energies up to 10-12 MeV/nucleon, which are difficult to reach at other facilities. At the present time, the availability of ^{252}Cf for this purpose is in question, in part due to competing commercial and security demands for this DOE-produced isotope.

An alternate and very powerful probe of new electroweak CP violation is to search for a *permanent electric dipole moment (EDM)* of an elementary particle or quantum bound state. The principles of quantum mechanics tell us that the interaction between an EDM and an applied electric field $\boldsymbol{E}$ is proportional to $\boldsymbol{S} \bullet \boldsymbol{E}$, where $\boldsymbol{S}$ is the spin of the particle or quantum system. This interaction is odd under both time reversal (T) and parity (P) transformations. By the CPT theorem of quantum field theory, a nonzero EDM implies the presence of CP violation. Other very promising experiments are also under development to search for atomic and electron EDMs. Certain radioactive atoms possessing a large octupole deformation are expected to have greatly enhanced sensitivity to CP-violating forces in the nucleus. Both ^{225}Ra and ^{223}Rn show promise as potential high-sensitivity deformed nuclei. Currently experiments

using these nuclei are being planned or pursued at laboratories around the world, including Argonne National Laboratory (using ^{225}Ra extracted from a ^{229}Th source at ORNL) and TRIUMF in Canada (using a radioactive beam). The precision of the ^{225}Ra experiment is projected to be limited by the isotope supply.

Neutrinoless double beta (0νββ) decay experiments could determine whether the neutrino is its own antiparticle, and therefore whether nature violates the conservation of total lepton number: a symmetry of the Standard Model whose violation might hold the key to the predominance of matter over antimatter. Multiple 0νββ experiments using different isotopes and experimental techniques are important not only to provide the required independent confirmation of any reported discovery but also because different isotopes have different sensitivities to potential underlying lepton-number-violating interactions.

CUORE - *the Cryogenic Underground Observatory for Rare Events* - is a bolometric detector searching for 0νββ in ^{130}Te. The Italian–Spanish–U.S. collaboration plans to install and operate TeO_2 crystals containing 200 kg of ^{130}Te at the underground Laboratori Nazionali del Gran Sasso in Italy. Replacing the natural Te with isotopically enriched material in the same apparatus would subsequently lead to a detector approaching the ton scale.

The Majorana collaboration is engaged in a research and development effort to demonstrate the feasibility of using hyperpure germanium (Ge) diode detectors in a potential one-ton-scale 0νββ experiment. The initial Majorana research and development effort, known as the Majorana Demonstrator, utilizes 60 kg of Ge detectors, with at least 30 kg of 86% enriched ^{76}Ge in ultralow background copper cryostats, a previously demonstrated technology. This Canadian–Japanese–Russian–U.S. collaboration is in close cooperation with the European GERDA Collaboration, which proposes a novel technique of operating Ge diodes immersed in liquid argon. Once the low backgrounds and the feasibility of scaling up the detectors have been demonstrated, the collaborations would unite to pursue an optimized one-ton-scale experiment.

Several other promising opportunities to carry out sensitive 0νββ experiments exist, and U.S. nuclear physicists have indicated an interest in being involved. One notable experiment is known as SNO+, a proposed ^{150}Nd-doped scintillator measurement that would utilize the previous Canadian hardware of the acrylic sphere, photomultiplier tubes, and support system–engaged in a coordinated international program of 0νββ measurements.

An isotope that is broadly used in nuclear physics as well as low temperature physics is ^{3}He. In addition, ^{3}He is widely used as a neutron detector. In particular, polarized ^{3}He is widely used as

an effective polarized neutron in scattering experiments, e.g., at Jefferson Lab. There are plans to implement a polarized ^{3}He source at BNL to provide polarized neutron beams at the Relativistic Heavy Ion Collider (RHIC). A beam of polarized ^{3}He is also a central element in the neutron EDM experiment, planned for the SNS.

Many unusual phases of matter like superfluidity, superconductivity, and Bose-Einstein condensation occur at extremely low temperatures, which enable study of subtle behaviors that are obscured by thermal motion at higher temperature. To reach a temperature below 0.3 K, one would need the ^{3}He-^{4}He dilution refrigerator, because it can operate continuously, provide a substantial cooling power at temperatures from around 1.0 K down to 0.010 K and below, and it can run uninterrupted for months. The ^{3}He-^{4}He dilution refrigerator is invaluable for experiments that require temperatures as low as 0.001 K because it can be used to pre-cool the adiabatic demagnetization systems.

There are many other scientific areas that require enriched isotopes. Mass differences between different isotopes cause sufficient change in bond strength and vibrational characteristics of volatile compounds of H, C, N, and O to affect their heat of vaporization. Thus, time, temperature, and geographical variations of isotope ratio differences can be used as a tracer of climate change, and help quantify the hydrogen, carbon, nitrogen, and oxygen cycle on earth. Sources of isotopes are essential as calibration standards.

For example, in *Paleoclimatology*, which studies climate change over the entire history of the Earth, oxygen isotope ratios[6] play an important role. Water with oxygen-16, $H_2{}^{16}O$, evaporates at a slightly faster rate than $H_2{}^{18}O$; this disparity increases at lower temperatures. The $^{18}O/^{16}O$ ratio provides a record of ancient water temperature. The measured heat capacity difference between $H_2{}^{18}O$ and $H_2{}^{16}O$ is 0.83 ± 0.12 J K^{-1} mol^{-1} for liquid water.[7] When global temperatures are lower, snow and rain from the evaporated water tends to be higher in ^{16}O, and the seawater left behind tends to be higher in ^{18}O. Marine organisms would then incorporate more ^{18}O into their skeletons and shells than they would in warmer climates. Paleoclimatologists directly measure this ratio in the water molecules of ice cores, or the limestone deposited from the calcite shells of microorganisms. Calcite, $CaCO_3$, takes two of its oxygen from CO_2, and the other from the seawater. The isotope ratio in the calcite found in the skeletons and shells of marine organisms is therefore the same as the ratio in the water from which the microorganisms of a given layer extracted, after readjusting for CO_2.

Nitrogen isotopic ratios also provide a powerful tool for evaluating processes within the nitrogen cycle and for reconstructing changes in the cycling of nitrogen through time. The biologically-mediated reduction reactions that convert nitrogen from nitrate (NO_3^{-1}, +5

oxidation state) to nitrite (NO_2^{-1}, +3) to nitrous oxide (N_2O^{+1}), to nitrogen gas (N_2^0), and to ammonia (NH_3^{-3}) are faster for ^{14}N than for ^{15}N as a result of higher vibrational frequency of bonding to ^{14}N than to ^{15}N .This results in products that are ^{15}N-depleted relative to the substrate. If the substrate reservoir is either closed or has inputs and outputs that are slow relative to one of the reduction processes then the reservoir will become enriched in ^{15}N. Therefore, the stable isotope ratio of nitrogen can be a promising proxy for delineating the *eutrophication* in the environment, which is a process describing an increase in chemical nutrients — compounds containing nitrogen or phosphorus — in an ecosystem. Since nitrogen is one of the important nutrient elements in a lake and abundant in anthropogenic sewage and chemical fertilizers, a range in fractionations of nitrogen isotope ratios in aquatic processes makes nitrogen isotope ratios an excellent tracer to monitor eutrophication.

In *astrophysics and planetary sciences*, measurements of D/H, $^{13}C/^{12}C$, $^{15}N/^{14}N$, or $^{18}O/^{16}O$ of primitive solar system materials record evidence of chemical and physical processes involved in the formation of planetary bodies and provide a link to materials and processes in the molecular cloud that predated our solar system. Modern developments exploiting nano-SIMS method have provided mineralogical and isotopic evidence of origins of stardust as composed of precursors of the solar system (McKeegan, et al, Science 314 (2006) 1724). Again, the isotope production requirements here are for measurement standards.

In *solid-state physics*, vibrational spectroscopy methods such as Brillouin light scattering, or Raman spectroscopy, plays a major role in using “isotope labeling”, in applications such as identifying the origins of meteorites, or magnitude of atomic displacements in a complex molecule. In superconductivity, shift in transition temperatures with isotopic substitution is a well-established approach to understand the mechanisms of formation of Cooper pairs, and their physical location inside complex crystals. Presence of mixed isotopes also acts as scattering centers in an otherwise perfect crystal, reducing cooperative behavior of atoms with substantially reduced thermal conductivity. Nuclei with unpaired spins can couple with electron spins, and the difference in decay time lends nuclear spin as a solid-state quantum memory. Isotopically enriched silicon or germanium-based semiconductors lend themselves for engineered nanostructures with phase coherence quality suitable for solid-state quantum memory devices. In chemistry, elusive transition states in reaction chemistry can be revealed through isotopic labeling. In exploiting the variations in a nuclear energy level between different isotopes lead to isotope-based spectroscopic methods, such as *Mössbauer spectroscopy*, which is a major research tool across many scientific disciplines. For example, decay of ^{57}Co, through an electron capture process to ^{57}Fe, provides an ideal parent/daughter relationship that lends itself to study in hyperfine interactions in magnetism, lattice dynamics, and local atomic structure in condensed matter in an unprecedented energy resolution of 10^{-13}

or better. Over 50,000 papers have been published in Mössbauer spectroscopy, and a total of 114 isotopes have been used. Today many of the parent/daughter isotopes are available only from a single country (not the U.S.), which is a cause for concern for the scientific community. Mössbauer isotopes are typically produced either in a cyclotron via deuterium bombardment or in a reactor.

In determining *fundamental constants and metrology*, developing a mass standard in fundamental units has been a struggle. The current approach, dubbed Avogadro's project, is an ongoing international collaboration between laboratories in Germany, Italy, Belgium, Japan, Australia, and USA to redefine the kilogram in terms of the Avogadro constant. The Avogadro constant is obtained from the ratio of the molar mass to the mass of an atom, and it is known to an uncertainty of 0.1 ppm. The goal is to reduce this to 0.01 ppm by measuring the volume and mass of isotopically pure silicon spheres. For a crystalline structure such as silicon, the atomic volume is obtained from the lattice parameter and the number of atoms per unit cell. The atomic mass is then the product of the volume and density. The limiting factors are the variability from sample to sample of the isotopic abundances of Si and the content of impurities and vacancies. Thus kilograms of isotopically pure ^{28}Si are needed, which is only provided by Russia. Currently two such 1 kg spheres are available. The new spheres were made from just one isotope: ^{28}Si. The mono-isotopic silicon was made in Russia while the near perfect crystal was grown in Germany, and perfect spheres were cut in Australia. To achieve the required concentration of the ^{28}Si isotope, a new centrifugal method was used for producing stable isotopes. SiF_4 of natural isotopic composition was used as a compound for centrifugal enrichment of ^{28}Si. A special centrifugal setup and a technology for production of $^{28}SiF_4$ with extremely high concentrations were developed in the Tsentrotekh-EKhZ Science and Technology Center. As a result, $^{28}SiF_4$ with an isotopic purity of 99.992–99.996% was produced.[6]

A very practical but important power-source type application is *radioisotope thermoelectric generators (RTG)*. Usage of RTG batteries can be very esoteric and unique. For example, they have been used as power source for spacecrafts (*Apollo, Pioneer, Viking, Voyager, Galileo, Cassini*), where a few hundred watts of power is needed for a very long time. They can also be used in very practical and large-scale applications like driving pacemakers and other implanted medical devices, where microwatts of power are needed. Various technologies are under development including stirling heat engines (devices that convert heat energy into mechanical power by alternately compressing and expanding a fixed quantity of air or other gas (the *working fluid*) at different temperatures), thermo-photovoltaic devices using piezoelectric materials combined with MEMS (micro electro mechanical systems) technology. The most suitable isotope for RTG applications is ^{238}Pu. It is an alpha emitter, thus it has the lowest shielding requirements and long half-life (87.7 years) high density (19.6 g/cc) and reasonably

high energy density (0.56 W/g). While there are concerns for environmental and other safety concerns, potential improvements in energy efficiency and prevention of radiation damage for some piezoelectric converters may increase the electric

al conversion efficiency by a factor 10 or more, thus making RTGs very attractive power sources and, in some cases, maybe the only alternative. Therefore, the need for alpha emitting isotopes of ^{238}Pu, ^{244}Cm, ^{241}Am, and beta-decaying ^{90}Sr will continue in the future.[7]

Table 9 lists the identified research opportunities, ordered by priority in the physical sciences and engineering areas. Within each opportunity, no particularly ordering of priority for individual isotopes has been assigned when more than one isotope is mentioned. The prioritizations are based on our own expertise and the priorities presented to NSACI from the DOE-ONP and DOE-BES programs. The relative priorities of items in Table 9 are discussed in the recommendations section. The lighter tone of blue in Table 9 highlights the relatively higher research opportunity potential of these topics. For example, the first four items of this table are the substance behind recommendations 3 and 4 of this report; "…the creation of a plan and investment in production to meet these research needs for heavy elements" and "…a focused study and research & development to address new or increased production of ^{3}He", respectively. The dark blue items are addressed in recommendation number 5 in support of research and development activities towards re-establishing a domestic capability for mass separated stable and radioactive isotopes.

Table 9: Research Opportunities in Physical Science and Engineering in order of relative priority.

Research activity	Isotope	Issue/action
Begin new facility to produce and study radioactive beams of nuclei from ^{252}Cf fission, for research in nuclear physics and astrophysics - CARIBU at ANL	^{252}Cf (2.6 yr)	Supply of ^{252}Cf is uncertain; 1 Ci source is needed each 1 ½ year for at least four years.
Measure permanent atomic electric dipole moment of ^{225}Ra to search for time reversal violation, proposed to be enhanced due to effects of nuclear octupole deformation;	^{225}Ra (15 d)	Supply of ^{225}Ra is limited. Need 10 mCi source of ^{225}Ra every two months for at least two years
Create and understand the heaviest elements possible, all very short-lived and fragile. Study the atomic physics and chemistry of heavy elements for basic research and advanced reactor concepts.	^{209}Po, ^{229}Th,^{232}Th, ^{231}Pa, ^{232}U, ^{237}Np,^{248}Cm, ^{247}Bk	Make certain actinides in HFIR and then prepare targets for accelerator-based experiments to make superheavy elements; targets needed are ^{241}Am, ^{249}Bk, ^{254}Es - not available now; need10 - 100 mg on a regular basis; purity is important
Neutron detectors, electric dipole moment measurement, low temperature physics,	^{3}He	Total demand exceeds that available
Isotope dilution mass spectrometers	^{236}Np, ^{236,244}Pu, ^{243}Am, ^{229}Th	High purity ^{236}Np is not available; others are in limited supply; 10 - 100 mg needed on a regular basis; purity is important
Search for double beta decay without neutrino emission - an experiment of great importance for fundamental symmetries	^{76}Ge	Need to fabricate large detectors of highly enriched ^{76}Ge; U.S. cannot produce quantity needed, ~1000 kg
Spikes for mass spectrometers	^{202,203,205}Pb, ^{206}Bi, ^{210}Po	^{202,205}Pb difficult to get in high purity in gram quantities
Avogadro project - worldwide weight standard based on pure ^{28}Si crystal balls	^{28}Si	Concern about future supply and cost of kg of material needed
Radioisotope micro-power source	^{147}Pm,^{244}Cm	Development needed for efficient conversion
Isotopes for Mossbauer Spectroscopy, over 100 radioactive parent/stable daughter isotopes	^{57}Co, ^{119m}Sn ^{67}Ni, ^{161}Dy, …	Some Isotopes only available from Russia, a concern for scientific community

Chapter 5: Research Opportunities with isotopes for national security and other applications

Isotopes are used in many areas related to nuclear security. DHS, NNSA, and the FBI require radioisotopes for the calibration and testing of instrumentation used for the analysis of nuclear materials. NNSA also performs nuclear physics measurements that utilize radioisotopes for these calibration and testing purposes. In addition these organizations use enriched stable isotopes for calibration and isotope dilution measurements in mass spectroscopy. All of these activities require relatively small amounts of these materials and there have been no difficulties in supplying these needs. In addition to these operational needs for sources there are some other activities that require larger quantities of materials or materials that are more difficult to obtain.

DHS is currently deploying many large radiation detection systems to monitor cargo that enters the United States. These devices measure both gamma-rays and neutrons and use this information to detect the presence of nuclear materials. The neutron detectors in these devices use ^{3}He tubes; this type of detector has excellent stability and high efficiency for detecting neutron radiation from plutonium. DHS plans on deploying a large number of these detectors in the course of the next five years. In a similar manner the "Second Line of Defense" program in NNSA/NA-25 will also deploy a large number of these same types of detection systems in foreign ports that ship cargo to the U.S. It would appear that the demands of these two programs will exhaust the U.S. reserve of ^{3}He and require more than the domestic annual production of this stable isotope.

However, this is not the only use of ^{3}He. As mentioned previously, the field of low-temperature physics uses ^{3}He in their dilution refrigeration systems that make all of their work possible. Also, polarized ^{3}He is used for magnetic resonance imaging for lung scans. *Therefore, this apparent shortfall of ^{3}He will not only hinder national security programs but will also have a devastating effect on the research and medical activities that rely on this isotope.*

In addition to the deployment of large detector systems, DHS is also conducting research on the effects of nuclear devices and "dirty bombs". This research uses radioisotopes of sufficiently long half-lives that are similar to those of interest to study the effects of radiation exposure to humans and the environment. Radiotracers with shorter half-lives have more easily detectable emissions and are preferable for research studies of their biologic or environmental disposition due to less potential waste problems. The research studies in this area will determine the most

effective method to decontaminate radioisotopes in the environment. This research will also help in the development of agents that could remove radioisotopes from an exposed individual.

DTRA, DHS, and NNSA are also involved in the nuclear forensics of a possible domestic nuclear event. The analyses involved with such forensics activities require the use of both stable and radioisotopes as tracers, such as ^{236}Pu, for the complex radiochemistry separations that are used in this analysis. For this application the quantities of the needed isotopes are modest and can be met by the existing inventories for the next several years.

The area of weapons physics also requires the use of isotopes. With the cessation of nuclear testing, the challenge for the national nuclear security program has been to certify the safety and reliability of the enduring stockpile. Central to this was the realization that the "parametric" engineering based development program that historically served the program well would have to be modified to have increased emphasis on a more fundamental scientific understanding of weapon performance. With the development of the modern ASCI based supercomputer capabilities it has become possible to computationally investigate the evolution of a nuclear explosion at an unprecedented level. However, this procedure will only result in a reliable predictive capability if commensurate effort is expended to insure that correct underlying physical data is used in the codes.

The nuclear processes occurring in the explosion are the fundamental heart of the device. A correct understanding of the nuclear reactions and their resultant radiation and particle transport must be accomplished. To this end, nearly every test has utilized "radchem" detectors to provide spatially resolved information on the device performance. The archived data from these tests represents a treasure of detailed information that can provide improved understanding of the underlying weapon physics. These radchem detectors have often been used to diagnose the 14 MeV neutrons produced in the thermonuclear reactions. In the high neutron fluence environment of a nuclear device, multiple nuclear reactions can occur on single radchem detector atoms. These higher order reactions often occur on radioactive isotopes for which little, if any, experimental data exist for their reaction cross sections. Since the radchem production is analyzed at times long compared with the explosion process, these materials are exposed to the complete integral fluence of the produced neutrons. In particular, as the neutrons evolve during the explosion dynamics they are down-scattered in energy eventually approaching some local environmental thermodynamic equilibrium. At these lower energies the dominant reaction becomes neutron capture. These "late time" effects can result in a perturbation of the isotopic abundances produced in the early thermonuclear burning of the device.

The interpretation of the device-produced isotopic yields is highly dependent on nuclear modeling. Though great improvements in the understanding of nuclear reactions have been made over the years, the a priori prediction of neutron capture cross sections remains very difficult. We could obtain improved data for capture cross sections on unstable species an experimental program has been launched that uses unique LANL capabilities. These include: (1) neutrons produced at Lujan Center at LANSCE; (2) a new detector system called DANCE (Detector for Advanced Neutron Capture Experiments) - a 4π 140 element BaF2 detector array to measure capture reactions: (3) capabilities for radiochemical processing of irradiation materials; and (4) a dedicated isotope separator (RSIS, Radioactive Sample Isotope Separator located in the CMR building) of radioactive species for target preparation. To complete this integral LANL program it is necessary to have a capability to produce the isotopes required for these measurements. The newly commissioned Isotope Production Facility can play a critical role in providing these required isotopes. This research program would therefore provide useful data for weapons physics as well as develop capabilities and experts in the area of isotope production and nuclear science.

While there are no high priority research opportunities identified in this security applications area, the following observations apply more broadly across the entire NIPA program.

- Nuclear security needs will exhaust our supply of ^{3}He, we recommend that DOE/NNSA and DHS should consider alternative materials or technologies for their neutron detectors.
- The Nuclear Security applications of isotopes will always benefit by those programs that maintain our domestic capabilities to produce isotopes.
- National Security interests would be served by the development of a domestic source for a wide range of stable isotopes rather than relying on sources in Russia.
- There is a growing need for more experts in radiochemistry and other technical areas related to isotope production. DOE needs to help universities produce more of these experts.
- DOE should be able to characterize the isotopes that they produce with respect to nuclear forensics.

Chapter 6: Recommendations for Charge 1

Compelling research opportunities were identified and presented in prioritized lists within the two areas of 1) biology, medicine, and pharmaceuticals, and 2) physical sciences and engineering. The third area 3) security applications did not have immediate research priorities

but made a number of observations and recommendations that apply more broadly for the entire NIPA program. While it is challenging to assess relative scientific merit across disciplines, we have identified the highest priorities for the most compelling research opportunities. These recommendations also define the relative priorities of opportunities in Tables 8 and 9.

There are compelling research opportunities using alpha-emitters in medicine. There is tremendous potential in developing far more effective treatments of cancers by the use of alpha-emitters in comparison to other radio-isotopes. Therefore, development and testing of therapies using alpha emitters are our highest priority for research isotope production for the medical field. This priority is reinforced by the potential need for rapid action due to the 2012 deadline for downblending of current DOE stocks of ^{233}U, a procedure that would eliminate its value as a source of ^{225}Ac.

1. **Invest in new production approaches of alpha-emitters with highest priority for ^{225}Ac. Extraction of the thorium parent from ^{233}U is an interim solution that needs to be seriously considered for the short term until other production capacity can become available.**

There is strong evidence for the potential efficacy of pairs of isotopes with simultaneous diagnostic/therapeutic capabilities. Table 8 of this report presents a prioritized list isotopes that have the greatest research potential in Biology, Medicine, and Pharmaceuticals. NSACI finds the research opportunities offered with these pairs of isotopes to be the second highest priority in identifying compelling research opportunities with isotopes. Many of these isotopes could be produced at existing accelerator facilities. We recommend the maximization of the production and availability of these isotopes domestically in the U.S. through investments in research and coordination between existing accelerators. The panel felt that such a network could benefit all areas of basic research and applications from security to industry. This should include R&D to standardize efficient production target technology and chemistry procedures.

2. **We recommend investment in coordination of production capabilities and supporting research to facilitate networking among existing accelerators.**

The basic physical sciences and engineering group prioritized research opportunities across various disciplines and a summary of this prioritization is given in Table 9. The availability of californium, radium, and other trans-uranic isotopes, the first three opportunities in Table 9, are particularly important for research.

3. **We recommend the creation of a plan and investment in production to meet these research needs for heavy elements.**

Experts in the nuclear security and applications areas strongly consider the vulnerability of supply from foreign sources to be of highest priority. This concern was echoed strongly by all members of the subcommittee in from medicine to basic science and engineering. Additionally, the projected demand for ^{3}He by national security agencies far outstrips the supply. This would likely endanger supply for many other areas of basic research. While it is beyond our charge, it would be prudent for DOE/NNSA and DHS to seriously consider alternative materials or technologies for their neutron detectors to prepare if substantial increases in ^{3}He production capacity cannot be realized.

4. **We recommend a focused study and R&D to address new or increased production of ^{3}He.**

The remaining isotopes in Tables 8 and 9 all are promising research opportunities, and funds for production from the Research Isotope Development and Production Subprogram would be well spent on targeted production of these isotopes to meet immediate research needs, especially if unique production opportunities arise. However, at this point in prioritization, NSACI concludes that larger, long-term issues should take priority. The darker tone of blue used in Table 9 is an indication of that.

An important issue for the use of isotopes is the availability of high-purity, mass-separated isotopes. The stable isotopes ^{76}Ge and ^{28}Si (^{3}He is stable but obtained from the beta-decay of ^{3}H, not by isotope separation) listed in Table 9 are needed in large quantities that present special problems. While no other individual stable isotope reached the level of the highest research priority, the broad needs for a wide range of mass-separated isotopes and the prospect of no domestic supply raised this issue in priority for the subcommittee. NSACI feels that the unavailability of a domestic supply poses a danger to the health of the national research program and to national security. NSACI recommends:

5. **Research and Development efforts should be conducted to prepare for the reestablishment of a domestic source of mass-separated stable and radioactive research isotopes.**

Vital to the success of all scientific endeavors is the availability of trained workforce. While the scientific opportunities have expanded far beyond the disciplines of radiochemistry and nuclear

chemistry, the availability of trained personnel remains critical to the success of research in all frontiers of basic science, homeland security, medicine, and industry. The individual research areas must make concerted efforts to invest in work-force development to meet these needs. The isotope program has a special responsibility to ensure a trained workforce in the production, purification and distribution of isotopes.

6. **We recommend that a robust investment be made into the education and training of personnel with expertise to develop new methods in the production, purification and distribution of stable and radio-active isotopes.**

All of the issues and recommendations considered here will be important input for answering the 2nd NSACI charge (See Appendix 1) due in 31 July 2009, developing a long range plan for the Nuclear Isotopes Production and Application Program.

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8. For example, the most popular Mössbauer radioactive parent isotope, ^{57}Co, is produced by irradiating an iron target with 9.5 MeV deuterons following ^{56}Fe(d,n)^{57}Co. After irradiation, the target is dissolved in mineral acids, followed by isopropyl ether extraction and an ion exchange separation. The next most widely used isotope, ^{119m}Sn, is produced through ^{118}Sn(n,γ)^{119m}Sn reaction or by electron capture decay of ^{119}Sb obtained from ^{119}Sn(p,n) ^{119}Sb or ^{120}Sn(2p,n) ^{119}Sb reaction (Spectroscopy Handbook, Ed. J. W. Robinson, CRC Press (1981)).

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Appendix 1: The NSAC Charge

August 8, 2008

Professor Robert E. Tribble
Chair, DOE/NSF Nuclear Science Advisory Committee
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Dear Professor Tribble:

The Fiscal Year (FY) 2009 President's Request Budget proposes to transfer the Isotope Production Program from the Department of Energy (DOE) Office of Nuclear Energy to the Office of Science's Office of Nuclear Physics, and rename it the Nuclear Isotope Production and Applications program. In preparation for this transfer, this letter requests that the Nuclear Science Advisory Committee (NSAC) establish a standing committee, the NSAC Isotope (NSACI) sub-committee, to advise the DOE Office of Nuclear Physics on specific questions concerning the National Isotope Production and Applications (NIPA) Program. NSACI will be constituted for a period of two years as a subcommittee of NSAC. It will report to the DOE through NSAC who will consider its recommendations for approval and transmittal to the DOE.

Stable and radioactive isotopes play an important role in basic research and applied programs, and are vital to the mission of many Federal agencies. Hundreds of applications in medicine, industry, national security, defense and research depend on isotopes as essential components. Over the years, individual communities and Federal agencies have conducted their own studies, identifying their needs in terms of isotope production and availability. Most recently, the DOE Office of Nuclear Energy and the Office of Science's Office of Nuclear Physics organized a workshop to bring together stakeholders (users and producers) from the different communities and disciplines to discuss the Nation's current and future needs for stable and radioactive isotopes, as well as technical hurdles and viable options for improving the availability of those isotopes.

The next step is to establish the priority of research isotope production and development, and the formation of a strategic plan for the NIPA Program, in which we expect NSACI to play a vital role. The NIPA's products and services are sold world-wide both to researchers and commercial organizations. The NIPA produces isotopes only where there is no U.S. private sector capability or when other production capacity is insufficient to meet U.S. needs. Commercial isotope

production is on a full-cost recovery basis. The following two charges are posed to the NSAC subcommittee:

Charge 1:

As part of the NIPA Program, the FY 2009 President's Request includes $3,090,000 for the technical development and production of critical isotopes needed by the broad U.S. community for research purposes.

NSACI is requested to consider broad community input regarding how research isotopes are used and to identify compelling research opportunities using isotopes.

The subcommittee's response to this charge should include the identification and prioritization of the research opportunities; identification of the stable and radioactive isotopes that are needed to realize these opportunities, including estimated quantity and purity; technical options for producing each isotope; and the research and development efforts associated with the production of the isotope. Timely recommendations from NSACI will be important in order to initiate this program in FY 2009; for this reason an interim report is requested by January 31, 2009, and a final report by April 1, 2009.

Charge 2:

The NIPA Program provides the facilities and capabilities for the production of research and commercial stable and radioactive isotopes, the scientific and technical staff associated with general isotope development and production, and a supply of critical isotopes to address the needs of the Nation. NSACI is requested to conduct a study of the opportunities and priorities for ensuring a robust national program in isotope production and development, and to recommend a long-term strategic plan that will provide a framework for a coordinated implementation of the NIPA Program over the next decade.

The strategic plan should articulate the scope, the current status and impact of the NIPA Program on the isotope needs of the Nation, and scientific and technical challenges of isotope production today in meeting the projected national needs. It should identify and prioritize the most compelling opportunities for the U.S. program to pursue over the next decade, and articulate their impact.

A coordinated national strategy for the use of existing and planned capabilities, both domestic and international, and the rationale and priority for new investments should be articulated under a constant level of effort budget, and then an optimal budget. To be most helpful, the plan should

indicate what resources would be required, including construction of new facilities, to sustain a domestic supply of critical isotopes for the United States, and review the impacts and associated priorities if the funding available is at a constant level of effort (FY 2009 President's Request Budget) into the out-years (FY 2009 – FY 2018). Investments in new capabilities dedicated for commercial isotope production should be considered, identified and prioritized, but should be kept separate from the strategic exercises focused on the remainder of the NIPA Program.

An important aspect of the plan should be the consideration of the robustness of current isotope production operations within the NIPA program, in terms of technical capabilities and infrastructure, research and development of production techniques of research and commercial isotopes, support for production of research isotopes, and current levels of scientific and technical staff supported by the NIPA Program. We request that you submit an interim report containing the essential components of NSACI's recommendation to the DOE by April 1, 2009, and followed by a final report by July 31, 2009.

These reports provide an excellent opportunity for the Nuclear Physics program to inform the public about an important new facet of its role in the everyday life of citizens, in addition to the role of performing fundamental research. We appreciate NSAC's willingness to take on this important task, and look forward to receiving these vital reports.

Sincerely,
Jehanne Simon-Gillo
Acting Associate Director of the Office of Science
for Nuclear Physics

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Appendix 3: Agendas of Meetings I, II, and III held by NSACI

NSAC Isotopes Subcommittee Meeting I

November 13-14, 2008

Hilton, Gaithersburg, Maryland

Thursday, November 13, 2008

9:00 Welcome

9:15 Charge from NSAC Chair – Robert Tribble

9:30: DOE-ONP perspective – Jehanne Simon-Gillo

10:00 Introduction – Don Geesaman

10:30 Break

10:45 Overview of the NE Isotopes Program – John Pantaleo

12:00 Lunch

1:30 Report from Isotopes Workshop – John D'Auria

2:15 Discussion of the charge and subcommittee perspective

3:30 Break

3:45 Industry perspective – Roy Brown

4:45 Discussion of the plan forward

5:30 Adjourn

Friday, November 14, 2008

9:00 Discussion of how to involve the broad community

10:00 Presentations of recent reports – Tom Ruth: National Academies Study

Robert Atcher: National Cancer Institute Study

11:30 Executive session

1:00 Adjourn

NSAC Isotopes Subcommittee Meeting II

December 15-16, 2008

Betheseda, Maryland

Monday, December 15, 2008

9:00 Introduction

9:45 OMB – Mike Holland

10:00 FBI – Dean Fetteroff

10:45 Break

11:00 National Institute of Biomedical Imaging and Bioengineering – Belinda Seto

12:00 Lunch

1:30 Department of Homeland Security/DNDO – Jason Shergur

2:10 DOE Office of Nuclear Physics – John D'Auria

2:50 DOE Office of Basic Energy Sciences – Lester Morss

3:30 Break

3:45 National Science Foundation – Brad Keister

4:30 Perspective – Jack Faught

5:00 Perspective – Kenny Jordan

5:30 Adjourn

Tuesday, December 16, 2008

9:00 National Cancer Institute – Craig Reynolds

9:40 NNSA – Victor Gavron

10:30 GNEP – Tony Hill

11:10 Executive session

1:30 Adjourn

NSAC Isotopes Subcommittee Meeting III

January 13-15, 2009

Rockville, Maryland

Tuesday, January 13, 2009

Input from Professional Societies and other groups on priorities for research

Speakers and organizations

9:00	Introduction
9:15	Sean O'Kelly, TRTR
10:00	Lynne Fairobent, AAPM
10:40	Break
11:00	Mark Stoyer, ACM/DNCT
11:40	J. David Robertson, MURR
12:30	Lunch
14:00	Gene Peterson, R&D for Accelerator Production of Isotopes
14:40	Scott Aaron, Stable Isotopes
15:30	Break
16:10	Roberto Uribe-Rendon, CIRMS
16:50	Robert Atcher, SNM

Wednesday, January 14, 2009

9:00	Michael Welch
9:40	Richard Toohey, HPS
10:30	Break
11:10-17:00	Executive Session

Thursday, January 15, 2009

9:00-16:00	Executive Session

Appendix 4: List of Federal Agencies Contacted by NSACI

Air Force Office of Scientific Research
Armed Forces Radiobiology Research Institute
Department of Agriculture
Department of Defense
Department of Energy - Fusion Energy Sciences
Department of Energy- National Nuclear Security Administration - Nuclear Non-proliferation
Department of Energy-Basic Energy Sciences
Department of Energy-Biological and Environmental Research
Department of Energy-Nuclear Physics
Department of Homeland Security
Environmental Protection Agency
Federal Bureau of Investigation
National Cancer Institute
National Institute of Allergy and Infectious Disease
National Institute of Biomedical Imaging and Bioengineering
National Institute of Drug Abuse
National Institute of Environmental Health Science
National Institute of General Medical Science
National Institute of Standards and Technology
National Science Foundation - Directorate for Engineering
National Science Foundation - Directorate for Mathematical and Physical Sciences
National Science Foundation- Directorate for Biological Sciences
Office of Naval Research
State Department
U. S. Geologic Survey

Appendix 5: List of Professional Societies contacted by NSACI

Academy of Molecular Imaging
Academy of Radiology Imaging
Academy of Radiology Research
American Association of Physicists in Medicine
American Association of Cancer Research
American Chemical Society
American Chemical Society - Division of Nuclear Chemistry and Technology
American College of Nuclear Physicians
American College of Radiology
American Medical Association
American Nuclear Society
American Nuclear Society - Division of Isotopes and Radiation
American Pharmacists Association - Academy of Pharmaceutical Research and Science (APhA-APRS)
American Physical Society
American Physical Society - Division of Biological Physics
American Physical Society - Division of Material Physics
American Physical Society - Division of Nuclear Physics
American Society of Clinical Oncology
American Society of Hematology
American Society of Nuclear Cardiology
American Society of Therapeutic Radiation and Oncology
Council on Ionizing Radiation and Standards
Health Physics Society
National Organization of Test, Research and Training Reactors
Radiation Research Society
Radiation Therapy Oncology Group
Radiochemistry Society
Radiological Society of North America
Society of Molecular Imaging
Society of Nuclear Medicine