THE PRODUCTION AND APPLICATION OF RADIOISOTOPES

- A CANADIAN PERSPECTIVE -

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ABSTRACT

This paper outlines the historical evolution of radioisotopes from first concepts and discoveries to significant milestones in their production and the development of applications throughout the world.

Regarding production, it addresses the methods that have been used at various stages during this evolution outlining the important findings that have led to further developments. With respect to radioisotope applications, the paper addresses the development of markets in industry, medicine, and agriculture and comments on the size of these markets and their rate of growth.

Throughout, the paper highlights the Canadian experience and it also presents a Canadian view of emerging prospects and a forecast of how the future for radioisotopes might develop.

INTRODUCTION

Radioisotopes have been in use for around 100 years, but the application of naturally occurring radioactivity was, and continues to be very limited - the use of radium for cancer therapy in the first half of this century being perhaps the only significant application. However, with the availability of man-made radioisotopes, firstly from cyclotrons in the 1930's and then from reactors in the 1940's, a new industry emerged. In the past 40 years the applications of radioisotopes have burgeoned to the point where these materials find applications in almost every aspect of human life. While the best known applications are in medical diagnosis and therapy, very few industrial sectors and research fields do not make some use of man-made radioactivity.

EARLY DEVELOPMENTS

The key to large-scale application of artificially-produced radioisotopes was the construction in several countries of high-flux nuclear reactors in the 10-year period after World War II. During this time a variety of nuclides became available and very quickly moved from research studies to routine clinical or industrial use. Iodine-131 was perhaps the most important medical isotope introduced at this time, and almost immediately found widespread utility in both diagnostic and therapeutic thyroid procedures. I-131 is still a widely used nuclide today. Phosphorus-32, mercury-203 and chromium-51 were also accepted medically with enthusiasm, but now 30 years later none of these are of any real clinical significance. Carbon-14, used in labelled compounds for research purposes, cobalt-60, as an external radiation source for cancer therapy, and iridium-192 and cesium-137 for industrial radiography and gauging, were also introduced in this period - all of these are among the most important isotopes in current use. During the next 20 years many other reactor nuclides, whether produced during fission processes or by bombardment of an appropriate elemental target, were evaluated for utility. Although very few experienced widespread commercial usage, five (tritium, molybdenum-99, iodine-125, xenon-133 and americium-241) have become very important for specific applications.

Although cyclotrons were the first sources of artificial radionuclides in the late 1930's, their importance for large scale production faded until the past 15 years when several neutron-deficient isotopes found significant diagnostic utility. Whereas reactors are able to produce such large quantities of isotopes that the entire world requirements for all commercial reactor-irradiated nuclides (except Co-60) could be met by 2 or 3 facilities comparable to Canada's NRU reactor, isotope-producing cyclotrons have relatively small capacities. Thus more than 20 cyclotrons are now in use on a full-time, dedicated basis world-wide, for the production of nuclides. New capacity is being added at the rate of about 2 cyclotrons per year. As a consequence of this much smaller unit productive capacity, cyclotron isotopes are generally much more costly than those originating in reactors. As an example, the bulk price of thallium-201 is of the order of $5/mCi at the end of processing, compared with $0.05/mCi for Mo-99, which has a comparable half-life, but a much more complex processing operation. Similarly, reactor-produced Co-60 is available in bulk for less than $2/Ci, while the shorter-lived cyclotron produced Co-57 sells for more than $40,000/Ci. Despite these higher costs cyclotron isotopes such as thallium-201, gallium-67 and iodine-123 have found widespread usage in applications where their unique properties provide benefits unobtainable with reactor nuclides.

CANADA'S ROLE

Canada has been the world's major supplier of reactor isotopes for many years, particularly dominating the production of Co-60 and Mo-99, the two most important commercial reactor isotopes. This position was achieved through an unbroken history of production and export, starting with I-131 produced in NRX in 1947, through to the current situation where irradiations are performed in NRU and 14 CANDU electricity generating reactors in Canada and off-shore. The Canadian role as an international supplier of cyclotron isotopes is much more modest as the first production scale accelerator only started up in 1982. However, Canada is now substantially self-sufficient in accelerator isotopes, and is a small, but significant exporter.

Atomic Energy of Canada Limited (AECL), Radiochemical Company, Canada's Isotope Production Company, has more than 30 nuclides in routine commercial production, with half-lives ranging from 13 hours (I-123) to 300,000 years (chlorine-36) and decay modes ranging from very low energy beta emission (C-14 and nickel-63), to high energy gamma (Co-60) and α-particle (polonium-210) emission. The products are marketed as radiochemicals, sealed sources and radiopharmaceuticals. AECL also manufactures and sells equipment to produce and utilize radioisotopes.

COMMERCIAL ISOTOPE PRODUCTION

Generally speaking, all significant commercial radioisotopes except Co-60 and Ir-192 require some kind of physico-chemical processing after irradiation. In addition, many require irradiation of either highly enriched isotopic materials, or targets specially prepared in specific, high purity chemical formulations. For these products the production processes frequently rely on classical inorganic chemical analytical procedures, since the physical quantities of material handled are usually quite low. In this respect isotope processing has not evolved materially over the past 30 years - the only significant development being widespread use of inorganic ion exchangers whose radiation resistance are particularly useful in preparations involving high radiation fields. In most other respects the chemical processes used tend to resemble laboratory-scale prototype operations rather than industrial manufacturing, despite the high dollar value of the products.

In addition to the reactors and cyclotrons used for irradiations and the shielded facilities used for processing, two other aspects of commercial isotope production bear mention. The first is the need for enriched stable isotope targets, most particularly in cyclotron operations. At present there are only two sources of these materials, both government agencies, in the United States and the Soviet Union. In recent years commercial producers throughout the world have expressed concerns about the long-term probability of obtaining these vital separated isotope targets from the existing suppliers at affordable prices. However, the limited markets for these products, and the substantial capital required for a new installation, provide very little incentive for the entry of a third, non-governmental supplier.

The second unique factor associated with isotope production is the need for radioactive waste disposal. Although the quantities of waste generated by isotope production activities are small and short-lived in comparison with wastes from nuclear power plants the disposal of irradiation capsules, in-process impurities, quality control samples, unsold product and contaminated hardware such as process equipment and ventilation system filters can be a major concern facing an isotope producer. The situations of each major isotope producer differ markedly due to such factors as location and national policies. AECL Radiochemical Company is fortunate in this respect, since its sister organization, AECL Research Company, operates a modern waste handling facility at Chalk River Nuclear Laboratories. Thus all radioactive wastes produced in the Ottawa isotope processing location are shipped to Chalk River in approved transport containers, for disposal or long-term storage, as appropriate. As part of an ongoing review of waste handling methods more segregation of wastes into high level/low level/long-lived/short-lived categories, together with decay in process units and compaction after decay, will be used increasingly to minimize the overall cost, and maximize disposal security.

SPECIFIC NUCLIDES
- PRODUCTION & APPLICATIONS

Table I lists the major commercial radioisotopes and their applications. All but two of these (Am-241 and Cs-137) are currently produced in large scale in Canada, though H-3 is not yet available for sale in commercial quantities. Following are specific comments on production, application and market aspects of the most significant nuclides for which Canada is currently a major world source.

Cobalt-60

In terms of total activity, dollars and market share, this isotope is the most important Canadian product. AECL pioneered the application of high specific activity Co-60 to cancer therapy 35 years ago using isotopes produced in research reactors. Subsequently, the large irradiation volumes available in CANDU reactor adjuster rods have been used to dramatically increase quantities of Co-60 available for both therapy, and such rapidly-growing industrial radiation processing applications as sterilization of medical disposable products and food preservation. Recent demand for Co-60 has been in the 20-30 MCi per year region, but with new market demands for food preservation and waste treatment production is planned to increase to more than 50 MCi per annum in the 1990's. At present Canada supplies more than 90% of total world demands and AECL Radiochemical Company has the capacity to supply economically much larger quantities.

AECL produces Co-60 in both pellet and slug form. Pellets offer a high degree of versatility for producing sources with a relatively high output from a small volume. Slugs on the other hand, are well suited to sources which should be relatively large in physical size, such as the "plaque" configuration generally utilized in large scale industrial irradiators. The targets for both products are produced by powder metallurgy from 99.9% cobalt powder, and then welded in a helium atmosphere into zircalloy capsules for reactor irradiation. Irradiation periods are generally 1-2 years in a flux of $1 - 2 \times 10^{14}$ $n\ cm^{-2}s^{-1}$.

Post-irradiation processing consists of Tungsten Inert Gas (TIG) welding the Co-60 slugs or pellets into stainless steel capsules according to customer size and curie content requirements. During processing, weld samples are removed and sectioned for examination of depth of weld penetration and to ensure freedom from defects. The welds on each irradiator source capsule are checked using a liquid dye-penetrant test capable of detecting surface flaws. All sources are wipe-tested to verify that they are free from contamination, and then measured.

Records are maintained of source serial number and measured content for the life of the source. The high level quality assurance program associated with Co-60 production ensures the integrity of the product. Co-60 sources used in AECL manufactured irradiation devices are guaranteed for 15 years, or nearly three half-lives, and to date, we have never had to replace a leaking source.

The plant and equipment required to process commercial quantities of industrial products with Co-60 gamma radiation is also designed, manufactured and installed by AECL. The plants are custom designed to meet each customers' needs, optimizing plant efficiency based on product density, dosage and throughput requirements.

Safety of operating personnel is a key factor in design, and in all plants redundant control systems are mandatory. To date, AECL has designed and built approximately 60% of all the industrial irradiation plants that have been constructed throughout the world, and there has never been a serious radiation accident in any AECL plant.

Molybdenum-99

Mo-99 is the most important isotope used for in-vivo medical diagnosis, although the patient is never actually treated with the nuclide itself. Mo-99, with a 66 hours halflife decays to Tc-99m, and this 6 hours halflife daughter possesses the most desirable collection of properties for nuclear medicine of any currently known isotope. It emits a single gamma photon with an energy ideal for current imaging instruments, can be combined in a variety of chemical compounds, each useful for visualizing different body organs or systems, and the short half-life minimizes patient radiation dose. Tc-99m for injection is separated chromatographically from Mo-99 by an ion-exchange process which provides the product in a sterile, apyrogenic, carrier free form in physiological saline solution. These technetium generators are dispatched to hospitals on a weekly basis, thus ensuring a low-cost, reliable supply of Tc-99m.

Until the early 1970's technetium generators were loaded with low specific activity Mo-99 produced by the (n,γ) reaction on enriched Mo-98. Rapidly-increasing hospital demand for Tc-99m in ever-increasing purity led to the introduction of fission product Mo-99 in 1972. AECL was one of the first manufacturers of this product and currently supplies about 60% of world requirements. To meet this volume 120-150 g of highly enriched U-235, in the form of a U-Al alloy, are irradiated in a neutron fluence of ~ 2 x 10^{20} ncm^{-2} each week.

Following a multi-stage separation process and rigorous quality control measurements, approximately 5,000 Ci Mo-99 are available for sale at the end of each production run, some 48 hours from reactor removal. At the present time, either three or four targets are processed each week depending upon such factors as customer demand, reactor shutdowns, actual fluxes and process yields. Although nuclear medicine usage of Tc-99m continues to increase steadily, the development of central pharmacies in the United States and elsewhere have resulted in significant improvements in Mo-99 usage efficiencies. Thus total world-wide Mo-99 demand increases are less than 5% per year at present, though there is a steady trend towards production of larger Tc-99m generators. No molybdenum carrier is added during the AECL production process, and specific activity measurements have confirmed that virtually no molybdenum is inadvertently added to the product from the stainless steel process equipment. Thus AECL's Mo-99 is particularly suited for use in large Tc-99m generators. Since the final product solution contains less than 10 parts per billion radioactive impurities a decontamination factor of more than 10^7 is obtained on a routine basis with relatively high chemical yield.

RCC's typical product form is sodium molybdate in 0.2 ± 0.05 N NaOH. Total batch activity is measured in-cell, and all other quality control is carried out on small samples. Activity concentration is determined by gamma spectroscopy, normality by potentiometric titration, and specific activity by polarography, the latter two procedures being carried out on decayed archive samples. Following chemical separations, radionuclidic purity is determined by gamma spectrometry (I-131, Ru-102, Te-132, Zr/Nb-95 and other gamma emitters) and liquid scintillation counting (Sr-89/Sr-90). Gross alpha contamination is determined by surface barrier detector. With the exception of the two archive analyses, all other Q.C. data is available shortly after completion of batch processing.

Iodine-125

The first significant commercial application of this nuclide was its use as a label for radioimmunoassay and thyroid hormone measurements in the early 1970's. These continue to be large consumers of I-125 to this day, but have been overtaken by its use in radiation sources for bone densitometry measurement, implantable therapy applications and X-ray fluorescence excitation. Current world demand for I-125 is 40-50 Ci/week, growing at 5-10% per year. I-125 is produced by neutron irradiation of xenon gas utilizing the reaction Xe-124 (n,γ) Xe-125 → I-125. Two major challenges arise in the production of this isotope. The reaction I-125 (n,γ) I-126 has a high cross-section, so continued irradiation to produce a reasonable yield of I-125 results in a product highly contaminated with 13-day I-126, an isotope which severely restricts I-125's use in source applications, and also impacts on its usage in the clinical laboratory. The usual practice is to decay the I-126 out of the product, down to less than 2% relative to I-125, though this is still a barely acceptable source fabrication level. AECL has developed a process which routinely produces an I-126 content in I-125 of less than 0.05%, without post-irradiation decay.

A second challenge relates to the need to irradiate large quantities of Xe-124 to produce the volume of I-125 required weekly. Until recently, AECL was able to use natural xenon gas in the large irradiation volumes available in the NRU reactor to produce the required quantities of I-125. However, as demand for this nuclide has grown, it has become necessary to irradiate costly enriched Xe-124 with the need for efficient target recovery during processing. With this system, and a dry distillation purification process, AECL's current production capability is in excess of 50 Ci/week. It is anticipated that the steadily increasing usage of I-125 sources, particularly in osteoporosis-related diagnosis, will require this level of production in the next 2-3 years.

Carbon-14

This isotope's utility in labelling organic compounds for chemical, biochemical and pharmacological research was recognized over 30 years ago, and its usage has continued to increase steadily. Consumption of C-14 labelled compounds is readily correlated with levels of support of biological research in developed countries. Recent emphasis on biotechnology has led to 15-20% annual increase in demand over the past two years, compared with 3-5% per year over the previous 10 years.

Current world demand is estimated at between 600 and 700 Ci/year, and AECL supplies approximately 65% of this. The production route for C-14 is an (n,p) reaction on nitrogen, and the primary problems associated with this relate firstly to the need to irradiate large target volumes in high fluxes for 3-5 years, and secondly the care needed to avoid contamination of the system with ubiquitous, naturally-occurring C-12, either during target preparation or post-irradiation processing.

AECL irradiates its targets in 3 metre-length NRU reactor rods each containing 15 kg AlN target. Some experimental work has also shown that C-14 could be produced in CANDU reactor adjuster rods, in a similar fashion to Co-60.

The target production process routinely produces material containing less than 100 ppm carbon, and in combination with long irradiation and processing in a carbon-free environment, this allows production of C-14 up to or better than 60 mCi/mM or 97 atom %. Since product grading and pricing are very dependent on specific activity the routine determination of specific activity by calculation from activity concentration is intermittently confirmed by mass spectrometry.

At present AECL produces only bulk C-14 as $BaCO_3$ or $CaCO_3$, and supplies this raw material to nearly all the world's major manufacturers of C-14 labelled compounds. Other applications of C-14 are quite insignificant in comparison with organic compound labelling, though increased use of the technique of interwell reservoir tracing for tertiary oil recovery may result in increased consumption of this isotope.

Iridium-192

Radioisotope radiography represented one of the earliest medical and industrial applications of radiation. Today, most of the industrial non-destructive testing usage of radioisotopes involves Ir-192 radiography. Source holders, which double as radiography cameras, have been developed to the point where they are relatively lightweight but provide adequate shielding, and allow rapid, serial radiographic exposures to be made in the field without the need for high voltage X-ray equipment, or indeed any electrical power at all. Despite these operational advantages world Ir-192 demand is flat at around 1.5 MCi/year. Canada has typically supplied between 10% and 20% of this market in recent years.

A typical radiographic source/camera contains over 100 Ci Ir-192, and provides a radiation field of 55 R/hr at 1 m with a focal spot length of 3mm. The source generally consists of a stack of Ir-192 foils 0.25 mm thick and 2.7 mm in diameter. Although there is some difficulty in handling these foils in a hot cell with substantial air flow, the major production concerns with Ir-192 revolve around several complicated irradiation questions. Natural iridium has a very high thermal neutron capture cross-section (900 b) which not only requires the use of very thin target material to reduce self-shielding but also dictates that the target foils be dispersed in a way to minimize shadowing. In addition, Ir-192 itself has an even higher cross-section (1100 b) for the (n,γ) reaction to produce Ir-193, so the optimum irradiation time depends upon flux and reactor operating history. With the fluxes available to AECL in NRU the average specific activity of the foils produced in a typical production run is 16 Ci/foil (~ 500 Ci/g). One batch of target is discharged from the reactor every 2 weeks. This material is either sold to other source manufacturers or used for source fabrication at AECL.

Because of attenuation of the relatively low energy emission (~ 330 KeV) within a stack of high density iridium metal, up to 12 foils may be needed to produce a source with a 100 Ci measured output. These sources are generally constructed with an inner, non-welded container, and an outer welded capsule. RCC has recently started welding the inner containment on capsules used in a pneumatic mode in recognition of the greater stresses applied to these sources. All source capsules are leak-tested, and dummy welds from each production run are sectioned. Cable-type sources are also pull-tested after crimping of the pig-tail connector.

Thallium-201

This radioisotope was introduced for myocardial imaging, as a potassium analogue, in the mid-1970's and very rapidly became the most widely used cyclotron-produced nuclide. In fact, the production of Tl-201 has been the prime justification for the installation of perhaps half of the cyclotrons currently in commercial production. The rapid acceptance of this isotope, which is produced by irradiation of a highly enriched Tl-203 target with 25-30 MeV protons, led to strong demand for Tl-203, resulting in rapid depletion of available target stocks, and raising concerns about the commercial responsiveness of government-controlled stable isotope production facilities. These fears have proved groundless as subsequent Tl-203 demand has fallen to a level more appropriate to steady-state production operations. The production of Tl-201 is a two-stage process requiring an initial separation of Pb-201 from the irradiated target followed by a Tl/Pb separation to produce the final product. In order to maximize yield of product with optimum shelf-life the control of incident beam energy, target thickness, and time parameters associated with both irradiation and chemical processing is critical. A production yield of 1.5 mCi/uA hr (as at the completion of second stage processing) is obtained by AECL.

World Tl-201 demand is increasing modestly from the current level of 700 Ci/week, but because of the inherent cost of the product, this nuclide is at risk for partial or complete displacement by the introduction of a competing Tc-99m-based myocardial agent.

Iodine-123

This short half-life (13 hr) nuclide has been recognized for many years as the agent of choice for many nuclear medicine procedures, limited only by reliable availability at acceptable cost and purity. Most material available until recently was produced by a (p,2n) reaction on Te-124. The clinical utility of this product is severely limited by relatively high I-124 contamination, resulting in both image degradation and excessive patient radiation dose. A much cleaner I-123 produced by the (p,5n) reaction on I-127 has been available for several years, but this method requires a costly 70-MeV proton accelerator. The relative scarcity of these devices has limited availability of this higher purity I-123. For these reasons world-wide I-123 usage has been quite modest, and this isotope has not developed to its true clinical potential.

At TRIUMF in Vancouver, Canada, AECL possesses a negative ion cyclotron capable of delivering a 200 µA 42-MeV external beam. This high intensity external beam has allowed AECL to develop a unique procedure for production of very high purity I-123 on a low energy cyclotron. Using a highly enriched Xe-124 target a patented process producing 8 mCi I-123 (at the end of processing) per µAh irradiation has been in routine production 5 days per week for over a year. Beam currents up to 100 uA have been used, and the final product is of substantially better radionuclidic purity than even the (p,5n) I-123. Batches of up to 12 Ci of I-123 have been produced by this process.

AECL believes this process which currently makes high purity I-123 available throughout North America, will lead to rapid development of I-123 labelled radiopharmaceuticals. Eventual demand for this form of I-123 is expected to require several dedicated cyclotrons strategically located world-wide to make the nuclide available routinely on the most cost-effective basis.

CONCLUSION

The worldwide demand for radioisotopes has grown steadily over the past 40 years. Radioisotopes provide many social and economic benefits and offer a better quality of life for many people. Present day applications of radioisotopes range from medical diagnosis and therapy to scientific and medical research to agricultural and commercial utilization. Promising radiation processing developments in areas such as food preservation and waste treatment combined with the encouraging clinical potential of many isotopes will increase the worldwide demand for radioisotopes in the 1990's.

More specifically, those areas of isotope usage which are believed to have most growth opportunities are food irradiation (Co-60 and Cs-137), in-vivo diagnosis with isotopically labelled monoclonal antibodies (In-111, Tc-99m, I-123) and in-vivo radiotherapy, using either monoclonal antibodies or other delivery systems, e.g., implants, linked to beta or alpha emitters (Y-90, Re-186/188, I-131, At-210, Pb/Bi-212).

TABLE I

ISOTOPE	HALF-LIFE	TYPE OF RADIATION	PRINCIPLE USES	ORIGIN
Cobalt-60	5.3 years	Gamma	- Sterilization - Food Irradiation - Waste Treatment - Industrial Radiography - Gauging Devices	Power and Research Reactors
Molybdenum-99	66 hours	Gamma	- Raw Material for Tc-99m (half-life 6 hrs) generator. Used in brain, bone, lung, kidney scans	Research Reactors
Thallium-201	73 hours	Gamma	- Cardiac Imaging	Cyclotron
Gallium-67	78 hours	Gamma	- Soft Tissue Tumor and Abscess Detection	Cyclotron
Americium-241	432 years	Alpha	- Smoke Detectors - Neutron Sources	Research Reactors
Tritium	12.3 years	Beta	- Labelled Compounds - Luminous Devices	Power and Research Reactors
Cesium-137	30 years	Gamma	- Gauging Devices - Industrial Radiography - Food Irratiation	Power Reactors
Iridium-192	74 days	Gamma	- Industrial Radiography - Pipeline Weld Inspection	Research Reactors
Xenon-133	5 days	Gamma	- Lung Scanning	Research Reactors
Iodine-131	8 days	Gamma	- Thyroid Imaging and Therapy	Research Reactors
Iodine-125	60 days	Gamma	- Clinical Lab Test Procedures - Radioimmunoassay	Research Reactors
Carbon-14	5,500 years	Beta	- Synthesis of Radioactive Organic Compounds for Biochemical, Biological and Chemical Research	Research Reactors
Iodine-123	13 hours	Gamma	- Thyroid Imaging - Experimental Nuclear Medicine - Brain and Heart Studies	Cyclotron