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Advances in the Production of Isotopes and Radiopharmaceuticals at the Atomic Energy Corporation of South Africa

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SUMMARY. Utilisation of the SAFARI-1 research reactor focussed on the production of isotopes over the past five years as part of the AEC's commercialisation programme. The technologies required for the production of a variety of isotopes have been developed, and a proven capability to produce significant amounts of fission product ^{99}Mo is considered to be the most significant achievement of this period. This capability is backed by a very flexible reactor operating schedule, local supply of fuel and target plates for ^{99}Mo production, modern hot cell facilities, an impressive support infrastructure at the AEC and quality assurance systems compatible with ISO 9000. The AEC can therefore make a positive contribution to the international isotope production technology.

1. INTRODUCTION

The Atomic Energy Corporation of South Africa Ltd. (AEC) owns and operates the 20 MW research reactor, SAFARI-1. Support infrastructure at the AEC include a manufacturing plant for MTR type fuel, control elements and target plates for ^{99}Mo production, modern hot cell facilities, a waste handling department, dry storage facility for spent fuel and a radioactive waste repository (1). A reactor theory division also lends valuable support through locally developed state of the art calculational software (2).

Utilisation of the reactor has in recent years changed from research and materials testing to the provision of irradiation services and the production of isotopes (1, 3). These range from the activation of gold and iridium wires for LDR brachytherapy, to isotopes which require sophisticated post irradiation processing, such as fission product ^{99}Mo.

The most important breakthrough achieved in recent years is the production of high quality fission ^{99}Mo, which has been done routinely since April 1993 and supplied to clients across the world. A capability for the reliable production of 1000 Ci of ^{99}Mo per week has been proven.

Facilities for the production of other isotopes such as ^{131}I (from fission), ^{32}P and ^{35}S are at various stages of completion. Extensive analytical methods have been developed and are routinely used to certify the quality of produced isotopes.

All AEC facilities, including the reactor and associated isotope production facilities, are licensed by the Council for Nuclear Safety, the South African nuclear regulatory body. Furthermore, all nuclear material is under IAEA safeguards. Quality assurance procedures based on ISO 9000 were developed for all aspects of the production of the various isotopes.

2. SAFARI-1

SAFARI-1 is a tank-in-pool type light water reactor of Oak Ridge design, with a 9 x 8 core matrix which currently contains 28 MTR type fuel elements and six control elements. The remaining lattice positions are either aluminium or beryllium reflector elements. The locally produced fuel elements consist of 19 flat plates constructed from uranium-aluminium alloy (90 wt% enriched in ^{235}U) clad with aluminium. A schematic representation of the core layout can be seen in Figure 1.

	1	2	3	4	5	6	7	8	9
A	A	B	P	P	B	B	B	B	A
B	A	B	F	F	F	F	F	I	B
C	A	B	M	F	C	F	C	F	A
D	A	B	F	F	F	F	F	M	B
E	A	B	M	F	C	F	C	F	H
F	A	B	F	F	F	F	F	M	B
G	A	B	M	F	C	F	C	F	H
H	A	B	F	F	F	F	F	B	A

F = Fuel Element   C = Control Element
M = ^{99}Mo production   I = Isotope Thimble
A = Al reflector   B = Be reflector
H = Hydraulic Facility   P = Pneumatic Facility

Figure 1: Schematic of SAFARI-1's current core configuration.

A seven-week operational cycle, which includes one shutdown week, is followed. The operating power is mostly dictated by commercial requirements (3). Depending on the power levels, one or more mid-cycle fuel reloads may be required. The operating history of SAFARI-1 since commissioning is represented in Figure 2.

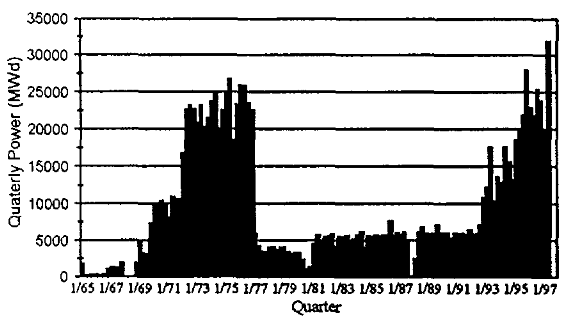

Figure 2: Quarterly Power History

The irradiation facilities at SAFARI-1 may be divided into the following broad categories:

- Reactor Poolside
- In-core irradiation positions
- Pneumatic Facilities
- Hydraulic Facility

The reactor poolside has the advantage that bulk samples can be irradiated in relatively high neutron fluxes without penetrating the reactor core and therefore at a reduced risk to the safety of the reactor. This facility is used for the neutron transmutation doping of silicon crystals and the colouration of topaz.

In-core irradiation positions have neutron fluxes of up to 2 x 10^{14} $n.cm^{-2}.s^{-1}$ at 20 MW and are primarily used for isotope production. Six positions are fitted with thimble tubes to allow sample retrieval while the reactor is on power. Five of these positions (C3, E3, G3, D8 and F8) are dedicated for the irradiation of uranium target plates for the production of fission product ^{99}Mo. The average neutron flux for these five positions is 1.5 x 10^{14} $n.cm^{-2}.s^{-1}$ at 20 MW.

The sixth thimble position (B8) is used for the production of isotopes with relatively short half lives, while the irradiation positions without thimble tubes (which can only be accessed when the reactor is shut down) are used for the production of isotopes with longer half lives.

The hydraulic facility also allows access to high flux positions while the reactor is on power. Gram quantities of target material can be irradiated for periods up to several weeks, with accurately controlled irradiation times.

The pneumatic facilities are mainly used for neutron activation analyses which involve shorter irradiations in lower flux regions, on smaller samples.

3. NTD SILICON

A facility for the neutron transmutation doping (NTD) of silicon single crystals (SILIRAD) was installed in the poolside of SAFARI-1 and commissioning started in the last quarter of 1992. This facility was designed for 103 mm diameter ingots and a few tons of these ingots have been irradiated successfully (4).

The SILIRAD was recently upgraded to accommodate 150 mm diameter ingots. The capacity of the facility was simultaneously increased by installing a double feed-through system, capable of accommodating ingot lengths of up to 600 mm.

Approximately two tonnes of silicon have already been irradiated on the upgraded facility. The feedback obtained from clients indicate that radial resistivity profiles are less than 2%, axial profiles less than 5% and target resistivities within 3%.

4. ISOTOPE PRODUCTION

Isotope production at the AEC can be divided into three broad categories:

- Irradiations with little or no post irradiation processing (^{198}Au, ^{192}Ir, ^{140}La)
- Isotopes requiring fairly straight forward post irradiation processing (^{35}S, ^{32}P, ^{125}I)
- Complex post irradiation processing (Fission ^{99}Mo and ^{131}I)

Technologies to produce a number of isotopes for the commercial market are currently being developed. These include ^{32}P and ^{33}P by irradiation of sulphur targets, ^{35}S from KCl targets, ^{125}I from ^{124}Xe, ^{90}Y from ^{90}Sr and ^{153}Gd from Eu targets. The recovery of ^{131}I from the fission ^{99}Mo process has also been developed and will be industrialised in the near future.

The use of alpha-emitting *in vivo* isotope generators such as ^{212}Pb/^{212}Bi is becoming more important in therapeutic nuclear medicine applications (5,6,7). These sources are, however, scarce and the possibility of producing them locally is being investigated.

The isotopes produced in SAFARI-1, routinely or ad hoc (as a service to a client or to support development work) are summarised in Table 1.

Table 1: Isotopes Produced in SAFARI-1

Routine	Ad hoc
^{99}Mo	
^{131}Ba	^{140}La
^{153}Sm	^{32}P
^{82}Br	^{90}Y
^{198}Au	^{35}S
^{131}I	^{79}Kr
^{192}Ir	^{125}I
^{41}Ar	^{117m}Sn
^{198}Au seeds	^{210}Po
^{90}Y wire	^{166}Ho
^{24}Na	
^{192}Ir wire	

4. FISSION PRODUCT ^{99}Mo

4.1 Irradiation of Target Plates

The five in-core irradiation positions dedicated to the irradiation of uranium target plates are equipped with thimble tubes which allow the insertion and retrieval of target plates with the reactor on power. The target plates are locally manufactured from a highly enriched uranium-aluminium alloy, clad with aluminium.

A maximum of seven target plates can be placed in an aluminium target plate holder and, depending on the order, irradiated for up to 200 hours. Each thimble tube is fitted with a self powered neutron detector. The data accumulated on the reactor's PC-based data logging system during irradiation can be accessed from the SAFARI-1 PC network. A comprehensive database of all irradiations, together with the yields obtained after processing at the Hot Cell Complex (HCC), is kept to continuously improve the planning accuracy.

4.2 Processing

Irradiated target plates are dissolved in concentrated sodium hydroxide. Nuclides of only a few elements are dissolved with molybdenum while the non-fissioned uranium is left as a solid residue for recovery at a later stage. The purification process has been designed to specifically ensure proper decontamination of ^{99}Mo, while at the same time giving good product recovery.

Purification of ^{99}Mo is carried out by means of two anion exchange resins and one chelating resin, all commercially available. The ammonium hydroxide eluate of the third column is filtered, evaporated to dryness, and redissolved in 0.2 M NaOH to convert the product into sodium molybdate. Sodium hypochlorite is sometimes added at this stage to ensure that the molybdenum is maintained in the molybdate form.

Dissolution of the irradiated target plates, separation and purification of ^{99}Mo, followed by quantification, dispensing and packaging of the final product, take place in five adjoining lead shielded hot cells.

Noble and other fission gases which are released during plate dissolution are adsorbed onto activated carbon in stainless steel columns. Complete backup capacity for all filtration systems is available.

Monitoring systems for noble gases, iodine, α and β/γ-emitters as well as hydrogen are distributed throughout the ventilation system for process control measures as well as the quantification of releases to the environment.

Alkaline liquid waste is accumulated in shielded stainless steel tanks and then immobilised in a cement-vermiculite mixture. Other acidic liquid waste solutions are accumulated and left to decay to levels where they can be transferred to the AEC's Nuclear Waste Management (NWM) Department (by underground pipeline) for further treatment.

Consumable solid materials used in the hot cell processes are contaminated with low levels of short-lived isotopes only. These materials are left to decay in hot cells or elsewhere in the facility to radiation levels where it can also be transferred to NWM for processing (8).

4.3 Production history

Fission ^{99}Mo has been produced routinely since April 1993 and supplied to a steadily growing number of clients across the world. The capability for the reliable production of 1000 Ci of ^{99}Mo per week, calibrated for six days after production, has been proven.

4.4 Drug Master Files

Drug Master Files for the AEC's fission ^{99}Mo have been submitted to and accepted by the pharmaceutical regulatory authorities in 22 European countries, Australia and Canada. A DMF, inter alia outlining the AEC's adherence to Good Manufacturing Practice, has also been submitted to the Food and Drug Administration in the USA.

5. RADIOPHARMACEUTICALS

5.1 Diagnostic

The AEC has been producing its own ^{99m}Tc generators together with a host of radiopharmaceutical kits for diagnostic nuclear medicine purposes for 25 years. Research into new diagnostic radiopharmaceuticals is ongoing and currently focussed on cancer imaging.

New bifunctional chelating agents selective for Tc and Re are being developed. A feature of the design of these ligands is that they may be linked to biologically active molecules such as peptides.

5.2 Therapeutic

The production of ^{153}Sm and ^{131}I (tellurium oxide route) has been operational for many years. Applications include ^{153}Sm-EDTMP for bone cancer pain palliation, ^{131}I-Lipiodol for liver cancer and ^{131}I capsules for thyroid treatment. To date, more than four hundred patients have participated in clinical trials involving ^{153}Sm-EDTMP (9-12). This has resulted in the AEC being granted a licence to market this drug known as Quadramet™. Much work has also gone into the understanding of the *in vivo* behaviour of lanthanide-containing bone-seeking radiopharmaceuticals (13-15).

The AEC also supports research into ^{186}Re-containing therapeutic agents at South African universities by supplying the isotope. Research into the use of ^{188}Re is also being carried out in conjunction with the Biomedical Research Centre in Pretoria.

Southern Africa, along with regions in South-East Asia, is a liver cancer "hot-spot". Rural populations are usually effected and prognosis is generally poor. Planning is under way to set up a multidisciplinary team to perform trials with the therapeutic radiopharmaceutical, ^{131}I-Lipiodol.

6. REGULATORY REQUIREMENTS

6.1 Council for Nuclear Safety

The safety of the reactor and personnel (at SAFARI-1 and the HCC) is carefully monitored by the local Council for Nuclear Safety (CNS). The Council's involvement spans normal operation of the reactor, production activities, routine maintenance and the licensing of new projects and facilities. A representative of the CNS visits facilities at the AEC at least weekly.

Safety analysis reports are submitted to the CNS before new facilities in the reactor or HCC are commissioned. These reports are substantiated with extensive risk assessments which include fault tree analyses according to international standards. The safety reports also address maintenance of the facilities, work instructions for operation of the facilities and personnel training.

6.2 IAEA

SAFARI-1 has been under IAEA safeguards since its commissioning in 1965. The AEC furthermore signed the nuclear nonproliferation treaty in 1991 and as such all its facilities and material are currently under IAEA safeguards. This also involves monthly inspections from the Agency, when a full audit of all material is performed, including fresh and spent fuel from SAFARI-1, target plates and waste.

Favourable reports have been received from the IAEA, indicating an acceptable state of the AEC's nuclear material and the systems to control it.

7. QUALITY ASSURANCE

Quality Management Systems (QMS) form an integral part of most operations at the AEC. The fuel manufacturing facility received ISO 9002 accreditation. The QMS at SAFARI-1 adheres to ASME NQA-1, but the system is currently being upgraded to adhere to ISO 9001. Accreditation will be requested towards the second half of 1998. The QMS for ^{99}Mo production at the HCC is being updated to conform to ISO 9002 requirements but accreditation has not yet been requested. The laboratory where the certification of product purity is performed, operates under ISO Guide 25.

8. ENVIRONMENT

The AEC's environmental management programme is aimed at adherence to the ISO 14000 system, which will be incorporated with the ISO 9000 system. The Corporation supports the principles of the Charter for Sustainable Business Development of the International Chamber of Commerce.

7. CONCLUSION

The Atomic Energy Corporation of South Africa has the unique capability to independently produce isotopes such as (most importantly) ^{99}Mo in a reliable high power research reactor with a proven safety record, operating on locally produced fuel. The reactor is supported by extensive local capabilities and infrastructure which include a modern hot cell complex and nuclear waste treatment facilities. The AEC can therefore contribute significantly to international isotope production technology.

8. REFERENCES

1. P.A. Louw, W.J. Strydom, A. Faanhof, G. Ball, A.M. Venter and F.C. de Beer. The Utilisation of the SAFARI-1 Research Reactor IAEA-SR-052, 1995
2. E.Z. Muller, G. Ball, W.R. Joubert, H.C. Schutte, C.C. Stoker and F. Reitsma. Development of a Core Follow Calculational System for Research Reactors, 9th Pacific Basin Nuclear Conference, 1994
3. D.W. Mingay. Commercialisation of the SAFARI-1 Research Reactor, IAEA/SR-183/44, 1993.
4. P.A. Louw, D.G. Robertson, W.J. Strydom. Neutron Transmutation Doping of Silicon in the SAFARI-1 Research Reactor, 9th Pacific Basin Nuclear Conference, 1994.
5. C. Wu, S. Mirzadeh, K. Kumar, D. Parker and O.A. Gansow. The Chemical Fate of ^{212}Bi Chelates Formed by $ß^-$ Decay of ^{212}Pb Chelates *Radioactivity and Radiochemistry* **3**, 1992, 18.
6. S.P. Hassfjell and P. Hoff. A Generator for Production of ^{212}Pb and ^{212}B , *Appl. Radiat. Isot.* **45**, 1994, 1021.
7. S.P. Hassfjell, P. Hoff, Ø.S. Bruland and J. Alstad. $^{212}Pb/^{212}Bi$-EDTMP Synthesis and Biodistribution of a Novel Bone Seeking Alpha-emitting Radiopharmaceutical, *J.Labelled Compounds and Radiopharmaceuticals* **34**, 1994, 717.
8. W. van Z. de Villiers. The management of radioactive waste from fission molybdenum-99 production, Spectrum '94 Nuclear and Hazardous Waste Management International Topical Meeting, Atlanta, 14-18 Aug. 1994.
9. A.S. Alberts, S.W. Brighton, P. Kempff, W.K.A. Louw, A. van Beek, V. Kritzinger, H.P. Westerink and A.J. van Rensburg. Samarium-153-EDTMP for Palliation of Ankylosing Spondylitis, Paget's Disease and Rheumatoid Arthritis.*J. Nucl. Med.* **36**, 1995, 1417.
10. W.K.A. Louw, I.C. Dormehl, A.J. van Rensburg, N. Hugo, A.S. Alberts, O.E. Forsyth, G. Beverley, M.A. Sweetlove, J. Marais, M.G. Lötter and A. van Aswegen. Evaluation of Samarium-153 and Holmium-166-EDTMP in the Normal Baboon Model, *Nucl. Med. Biol.* **23**, 1996, 935.
11. A.S. Alberts, B.J. Smit, W.K.A. Louw, A J van Rensburg, A. van Beek, V. Kritzinger and J. S. Nel. Dose response and multiple dose efficacy and toxicity of Samarium-153-EDTMP in Metastatic Cancer to Bone, *Radiotherapy and Oncology* **43**, 1997, 175.
12. I.C. Dormehl, W.K.A. Louw, F.H.A. Schneeweiss, U.M. Carl, G. Schmitt and S.A. Croft. Uptake of Ethylenediamine-tetramethylene Phosphonic Acid in Normal Bone After Multiple Applictions - A Primate Study, Accepted for publication: *Arzneimittel-Forschung/Drug Research* '97.
13. J.M. Wagener and N.V. Jarvis. Complexation of Trivalent Lanthanides by Ethylenediamine-tetramethylenephosphonate (EDTMP), *S. Afr. J. Chem.* **48**, 1995, 85.
14. N.V. Jarvis, J.M. Wagener and G.E. Jackson. Metal-ion Speciation in Blood Plasma as a Tool for Elucidating the *in vivo* Behaviour of Radiopharmaceuticals containing ^{153}Sm and ^{166}Ho, *J. Chem. Soc. Dalton Trans.*, 1995, 1411.
15. J.R. Zeevaart, N.V. Jarvis and G.E. Jackson. Blood Plasma Modelling of the *in vivo* Behaviour of Bisphosphonate-Metal-ion Complexes as Radiopharmaceuticals, Accepted for publication in *S. Afr. J. Chem.*, 1997.