Production and Supply of Molybdenum-99[1]

A. Background

Over 80% of diagnostic nuclear medical imaging uses radiopharmaceuticals containing technetium-99m (^{99m}Tc), entailing over 30 million investigations per year. The excellent nuclear characteristics of ^{99m}Tc enable high quality images with low radiation doses to patients. Its chemical characteristics make it very versatile for attaching to different chemical substances, so that it can be used to target different organs and diseases as required by different diagnostic procedures. The two most widely used ^{99m}Tc-based procedures are for imaging blood flow to heart muscles (myocardial perfusion imaging) and mapping the spread of cancer to bones (skeletal metastases imaging). The medical use of ^{99m}Tc has grown significantly in the past several decades, and moderate overall growth of 3–5% per year is expected to continue, with particular growth in countries expanding healthcare programmes. The IAEA is particularly active in helping developing countries to expand their use of ^{99m}Tc-based imaging procedures.

With a half-life of only six hours, ^{99m}Tc must be produced near the place and time it is to be used. It is produced by the decay of molybdenum-99 (^{99}Mo), which has a half-life of 66 hours. Production is carried out with a ^{99}Mo-^{99m}Tc generator either in the hospital where the ^{99m}Tc will be used or in a radiopharmacy. ^{99}Mo-^{99m}Tc generators are devices that help perform simple and reliable separation of ^{99m}Tc from ^{99}Mo of very high specific activity (e.g. fission-product ^{99}Mo, ~10^4 curies per gram (Ci/g)) adsorbed on an acidic alumina column. The ^{99m}Tc is obtained by passing physiological saline (0.9% NaCl solution) through the alumina column. Compact generators are available that deliver high quality ^{99m}Tc.

Over 95% of the ^{99}Mo required for ^{99m}Tc generators is produced by the fission of uranium-235 targets (^{99}Mo fission yield 6.1%) in nuclear research reactors (steps 1 and 2 in FIG. VII-1). The irradiated targets are then processed (step 3) and the resulting purified ^{99}Mo solution subsequently distributed for use in the production of ^{99}Mo-^{99m}Tc generators.

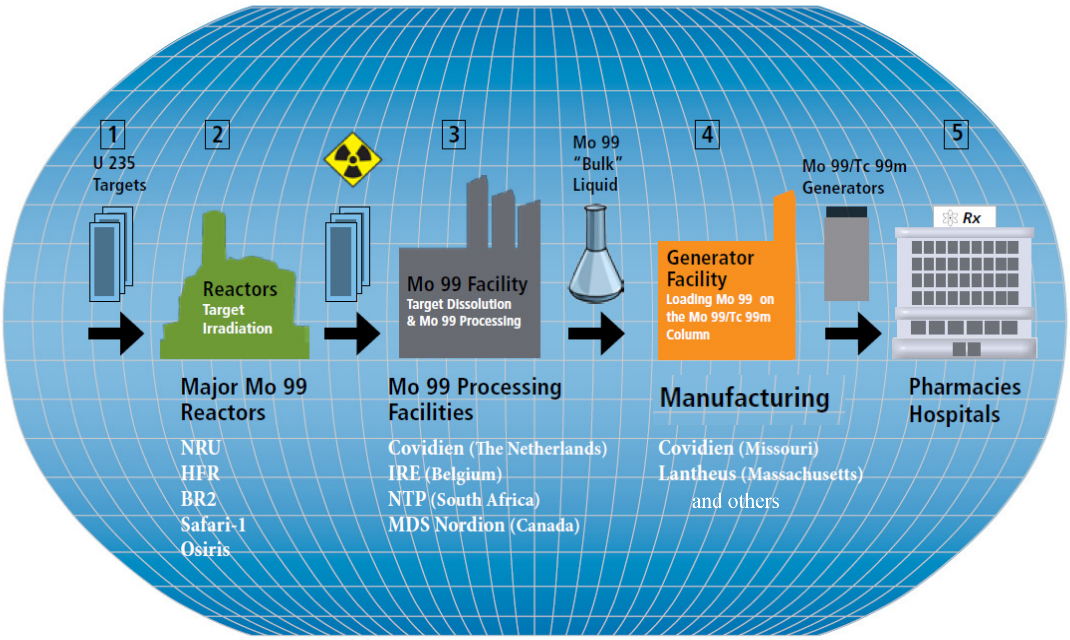

FIG. VII-1: Global supply chain of ^{99}Mo and subsequent utilization schematics. Source: www.covidien.com (October 2009)

[1] This annex to the *Nuclear Technology Review 2010* was prepared based mostly on the situation at the beginning of February 2010. Since the situation is continuously changing, some updates as of May 2010 have been added. The additions are, however, not comprehensive.

Since the last quarter of 2007, the supply chain shown in FIG. VII-1 has suffered from serious repeated disruptions in the production of ^{99}Mo. This annex summarizes the current status of global ^{99}Mo supplies as well as the reasons for recent disruptions. It summarizes the possibilities being considered to address these disruptions and the status of current deliberations. The IAEA is one of several organizations that can help coordinate deliberations to raise the likelihood, speed and efficiency of joint action to increase reliable supplies of ^{99}Mo. This annex also summarizes some of the recent IAEA activities to that end.

B. Production of ^{99}Mo

Five research reactors produce most of the world's ^{99}Mo (see Table VII-1). These reactors use highly enriched uranium (HEU) targets, and all are over 40 years old (see FIG. VII-2). As of 2009, NRU in Chalk River, Canada, was 52 years old; BR-2 in Mol, Belgium, was 48; HFR in Petten, the Netherlands, was 48; Osiris in Saclay, France, was 43; and Safari-1 in Pelindaba, South Africa, was 44. Moreover, none of these reactors is entirely dedicated to the production of ^{99}Mo and other radioisotopes. They all provide multiple services to multiple users.

In addition to the five major producers, the National Atomic Energy Commission (CNEA) of Argentina has been producing ^{99}Mo since 2002 using low enriched uranium (LEU) targets. CNEA's production record is an important demonstration of the use of LEU targets, even though its production represents only 1.5% of the global market. Indonesia also produces small quantities of ^{99}Mo for domestic use and some for export, for example to Bangladesh.

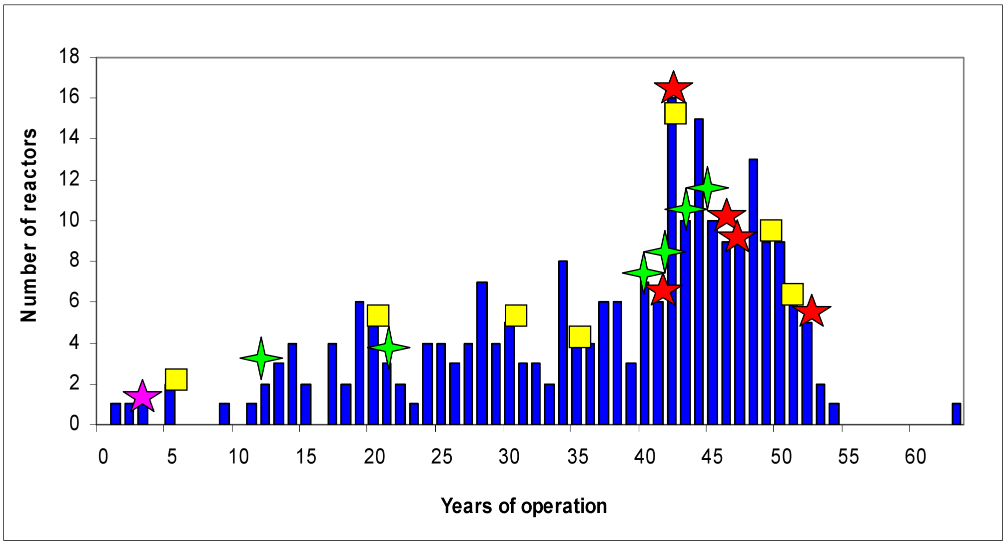

FIG. VII-2: Age distribution of the world's 245 operational research reactors. Source: IAEA Research Reactor Database. ★ The five major research reactors currently producing ^{99}Mo; ★ The OPAL research reactor (Australia); ✦ Existing research reactors that are already used by regional ^{99}Mo producers or for which commissioning is underway; □ Existing research reactors which are now studying the feasibility of providing irradiation services. See Tables VII-1 and VII-2 for more information.

There are currently only four large-scale facilities for processing the irradiated targets after they are removed from the reactors. Two processing methods are used, one involving acidic dissolution of the targets and the other involving alkaline digestion of the targets. Both require a series of radiochemical separation and purification steps that are very complex and require sophisticated technical skills and well-equipped hot cells. Purity requirements for ^{99}Mo are very high, and extensive quality controls are essential. The demanding requirements for robust operational systems, a reliable well-trained workforce, and excellent quality management systems, together with the expense of the required technology, have best been met by commercial corporations. The four ^{99}Mo processing facilities are, as shown in FIG. VII-1, operated by MDS Nordion in Canada, the Institute for Radioelements (IRE) in Belgium, Covidien in the Netherlands, and Nuclear Technology Products (NTP) in South Africa. Their typical production shares prior to the recent production disruptions were 40%, 20%, 25% and

10% respectively. A new facility, associated with Australia's OPAL reactor, is expected to become available in 2010. It completed trial production runs in 2009 and obtained regulatory approvals for regular production. It will be the first large-scale ^{99}Mo producer to use LEU targets and will have a production capacity of over 1000 Ci per week[2]. This is a bit more than 8% of the global market's weekly ^{99}Mo requirement of approximately 12 000 Ci.

The next major step in the chain is the production of ^{99}Mo-^{99m}Tc generators (step 4 in FIG. VII-1). This has become a well-established business in a number of countries, and there are many more enterprises at this step in the chain than at the previous steps. In addition to major corporate producers, such as Lantheus Medical Imaging, GE Healthcare, Daiichi, and Covidien; the Nuclear Energy Research Institute (IPEN) in São Paolo, Brazil, the Institute of Atomic Energy in Poland, and the Atomic Energy Organization of Iran in Teheran currently produce batches of a few hundreds of generators per week. Private initiatives in generator production have also emerged in Argentina, Chile and Turkey. All these centres depend on weekly imports of fission product ^{99}Mo.

Table VII-1: Fission-based ^{99}Mo production at research reactors worldwide

Existing research reactors used by large-scale producers						
Country	Name	Thermal power, MW	Thermal neutron flux, n/s/cm^2	Target type	Maximum annual operation, days[3]	Typical share of production %
Canada	NRU	135	4.0e14	HEU	315	40
Netherlands	HFR	45	2.7e14	HEU	290	30
Belgium	BR-2	100	1.0e15	HEU	115	10-15
South Africa	Safari-1	20	2.4e14	HEU	315	10-15
France	OSIRIS	70	1.7e14	HEU	220	5-8
Australia	*OPAL*	*20*	*3.0e14*	*LEU*	*340*	*yet to enter market*
Poland	*MARIA*	*30*	*3.5e14*	*HEU (for Covidien)*	*200*	*not known*

Existing research reactors used by regional producers						
Country	Name	Thermal power, MW	Thermal neutron flux, n/s/cm^2	Target type	Maximum annual operation, days[4]	Potential production capacity (weekly) 6-day Ci
Argentina	RA-3	5	4.8e13	LEU	230	200 Ci
Indonesia	GA SIWABESSY MPR	30	2.5e14	HEU/LEU conversion underway	147	150 Ci

[2] These are '6-day curies', meaning they are the number of curies six days after the end of the production process, which is generally eight days after irradiation in the reactor is completed.
[3] Source: IAEA Research Reactor Database (http://www.iaea.org/worldatom/rrdb/); National Research Council of the National Academies, 2009.
[4] Source: IAEA Research Reactor Database (http://www.iaea.org/worldatom/rrdb/)

Russia	WWR-TS	15	1.8e14	HEU	190	not known
Russia	IRT-T	6	1.4e14	HEU	190	not known

Existing research reactors to be used by regional producers (commissioning is underway)						
Country	Name	Thermal power, MW	Thermal neutron flux, n/s/cm^2	Target type	Maximum annual operation, days[5]	Potential production capacity (weekly) 6-day Ci
Egypt	ETRR-2	22	2.8e14	LEU	294	250 Ci
Pakistan	PARR-1	10	1.7e14	not known	Data not available	not known

An alternative to the fission-based production of ^{99}Mo shown in FIG. VII-1 is ^{99}Mo production through neutron activation of molybdenum trioxide targets in research reactors. This produces ^{99}Mo of relatively low specific activity, on the order of 0.2 to 1 Ci/g (7.4 to 37 GBq/g), depending upon the neutron flux. This product is popularly known as (n, gamma) ^{99}Mo and has been in limited use (1-2%) for producing ^{99m}Tc either through a process known as zirconium molybdate – ^{99}Mo gel generator (e.g. in China, India and Kazakhstan) or through a process using solvent extraction (e.g. in India). A facility in Chengdu, China, was the first large scale producer of gel generators and has provided up to 25% of national ^{99m}Tc requirements. Since 2006 India has produced more than 100 batches of gel generators using up to 28 Ci (1040 GBq) ^{99}Mo per batch and meeting nearly 15% of India's overall ^{99m}Tc needs. The maximum number of generators per batch is 24 and the maximum radioactivity capacity is about 1.2 Ci (44 GBq). Kazakhstan has been using the gel procedure for centralized production of ^{99m}Tc in Almaty, while development of portable generators is in progress.

Table VII-2: Existing research reactors with feasibility studies underway to provide irradiation services to produce fission-based ^{99}Mo

Country	Name	Thermal power, MW	Thermal neutron flux, n/s/cm^2	Target type	Maximum annual operation, days[4]	Potential production capacity (weekly) 6-day Ci
Germany	FRM-II	20	8.0e14	HEU (for IRE)	245	3000-4000 Ci
Canada	MNR MCMASTER UNIV	3	1.0e14	HEU	250	~1500 Ci
USA	MURR UNIV. OF MISSOURI	10	6.0e14	LEU	312	~3000 Ci
Chile	RECH-1	5	7.0e13	LEU	50	250 Ci
Czech Republic	LVR-15 REZ	10	1.5e14	HEU (for IRE)	210	not known
Poland	MARIA	30	3.5e14	LEU	200	not known

[5] Source: IAEA Research Reactor Database (http://www.iaea.org/worldatom/rrdb/)

Country	Name	Thermal power, MW	Thermal neutron flux, n/s/cm^2	Target type	Maximum annual operation, days[4]	Potential production capacity (weekly) 6-day Ci
Romania	TRIGA II PITESTI	14	3.3e14	LEU	280	~3000 Ci

C. Disruptions in ^{99}Mo supplies and follow-up initiatives

Starting in the last quarter of 2007, several independent reactor shutdowns and outage extensions significantly disrupted global ^{99}Mo supplies. These included the extension of a planned outage at NRU in 2007 related to regulatory commitments, the extension of a planned outage at HFR-Petten in 2008 due to leaks, the prolonged shutdown of NRU from May 2009 through at least late July 2010 to repair leaks, and an unplanned shutdown of the IRE processing facility in 2008 due to an iodine-131 release from the waste stream. These unplanned events, combined with other planned outages created a worldwide ^{99}Mo supply crisis.[6] BR-2 and Safari-1 generally functioned well during the crisis without any unplanned outages, and good cooperation among producers and reactor managers helped to reduce the crisis's impact. Operating producers increased production to the extent possible, for example, at Safari-1 when NRU and HFR were shutdown and at Covidien when IRE was shutdown. Nonetheless, in 2008, disruptions, i.e. cancellations or delays in patient services, ranged from 20% to 70% of planned services, depending on the week and location.

The ^{99}Mo supply chain will continue to remain fragile as long as it continues to rely on the same five aged production reactors. Some short term adjustments are possible. BR-2 will add one additional three-week cycle in 2010 to its normal schedule of reactor cycles, an addition made possible through resources contributed by manufacturers of ^{99}Mo-^{99m}Tc generators. The operating organizations of OPAL, HFR and Safari-1 have formed a cooperative group to improve operational reliability. The group is focused on non-commercial aspects of reactor operation. Operating experiences are openly shared and related challenges are discussed in depth. The formal agreements include cost recovery arrangements for resource sharing for technical support and peer review. Each facility has already taken advantage of assistance available from the others and offered assistance when asked. The initiative has also been positively received by the relevant regulatory bodies, which themselves have increased their interaction since the formation of this group.

Another short term response to the crisis was a series of meetings to discuss the difficulties of a long term solution and to map ways forward. These included expanding the scope of a 2008 Research Coordination Meeting of the IAEA CRP on 'Developing techniques for small scale indigenous ^{99}Mo production using LEU fission or neutron activation', discussions in Brussels in 2008 between the European Association of Nuclear Medicine (EANM) and relevant EU authorities on prospective EU actions, an IAEA side event in 2008 at EANM's annual meeting, a meeting of the International Nuclear Regulators Association (INRA) in 2008, a 2009 meeting hosted by the French Nuclear Safety Authority (ASN) for its counterparts from Australia, Belgium, Canada, Netherlands, South Africa, UK and USA, and a 2009 workshop on 'Security of supply of medical radioisotopes' held in Paris at the request of Canada by the OECD/NEA. Of particular concern to regulators was their dilemma in balancing health concerns and nuclear safety concerns in the event of unplanned outages. One consequence of the Paris workshop was the establishment, by OECD/NEA, of the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR). The IAEA is an observer in this group. The group held its first meeting in June 2009, at which it developed an action plan that included: addressing enhanced coordination among stakeholders and transparency in schedules, launching an economic analysis, and identifying possible options for additional capacity including through addressing transport related issues. One further short term response was a survey and report,

[6] HFR-Petten has been shut down since the third week of February 2010 and is expected to remain shut until August.

by the Association of Imaging Producers and Equipment Suppliers in November 2008, on molybdenum-99 production for nuclear medicine 2010–2020[7].

The longer term challenges, as discussed in these meetings, are several. Osiris is expected to shut down in 2015, and NRU will need a licence renewal in 2011. The Canadian Government has emphasized its support for the licence renewal but has also indicated that there may be no more reactor support beyond 2016. The report of the four-member panel of the Canadian Government released in December 2009 recommends, as the preferred option, a new research reactor devoted partially to radioisotope production. It also notes that the direct production of ^{99m}Tc using available medical cyclotrons, although possibly not economically attractive, can be an option for the immediate future.[8]

The European Commission has also responded to calls from its members to address the reliability of ^{99}Mo supplies in Europe. Following a number of meetings and studies to assess the situation, the Council of the European Union adopted conclusions in December 2009 calling for actions on ten points, including the coordination of efforts with other forums such as the HLG-MR and the IAEA.

As noted earlier, none of the five major reactors that produce ^{99}Mo is entirely dedicated to the production of ^{99}Mo. They were financed and built to provide multiple services to multiple users and not according to any business model designed to best serve the ^{99}Mo market. Indeed the business case for building new reactors for ^{99}Mo production is problematic. Margins are low, capital costs are high, lead times are long, and shipment denials and delays add market uncertainty, while the established existing competition, because of its history and other non-^{99}Mo activities, has government support, additional funds and no high capital costs to worry about. As will be discussed later, however, the cost of ^{99}Mo is only a small fraction of the cost of the final radiopharmaceutical dose administered to the patient. Thus, raising the price of ^{99}Mo, which might strengthen the business case in building more buffer capacity in ^{99}Mo production through additional investment, should be possible without significantly adding to the cost of the final radiopharmaceutical.

In addition to the currently weak business case for new capacity, recent experience in efforts to add new capacity has not been encouraging. In May 2008, AECL cancelled the Canadian MAPLE project, which included two reactors dedicated to ^{99}Mo production — each capable of meeting most, if not all, of global ^{99}Mo demand. The cancellation was due to commissioning challenges related to the design of the reactor core. In Australia, commissioning of the new OPAL reactor was interrupted by a ten-month shutdown following the discovery of dislocated fuel plates during operation.

Nonetheless, there are a few prospective new sources of production in the pipeline. As noted earlier, ^{99}Mo production in the Australian OPAL research reactor is scheduled to become available during 2010. Production from the MARIA reactor in Poland based on the irradiation of HEU targets (for Covidien, Petten, NL) was begun in March 2010. In May, similar irradiation of HEU targets began at the Řež reactor in the Czech Republic for production at IRE's facility in Fleurus, Belgium. The FRM-II reactor in Germany is also progressing on a project to produce ^{99}Mo via HEU target irradiation by 2013 (for IRE, Fleurus, Belgium). Two additional new multi-purpose research reactors are also expected to come on line soon: JHR at Cadarache, France, in 2015 or shortly thereafter and PALLAS in the Netherlands in 2016 or later, depending on the project schedule, which has yet to be finalized. These are expected to ensure sustainable ^{99}Mo production capacity when some of the currently used reactors may be shutdown. In the USA, there are two new LEU based production initiatives, one from the University of Missouri Research Reactor (MURR) and the other from the Babcock and Wilcox Company and Covidien. Prompted by the ^{99}Mo crisis and the USA's total dependence on ^{99}Mo imports, the US Congress passed the American Medical Isotopes Production Act of 2009, which envisages spending nearly $163 million over the next five years to establish a non-HEU domestic ^{99}Mo production process. Funding will come from the Global Threat Reduction Initiative (GTRI).

There is also scope for making greater use of the existing smaller scale production capacity noted earlier. For example, CNEA in Argentina plans to double its current production capacity. The National

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[7] Available at http://www.vrom.nl/Docs/milieu/200902_AIPESMolySupplyReport.pdf.

[8] In June 2009, the Canadian Government formed a four-member expert panel to review and recommend measures for meeting medical isotope production demands. The panel's report, released in December 2009, is available at http://nrcan.gc.ca/eneene/sources/uranuc/pdf/panrep-rapexp-eng.pdf.

Nuclear Energy Agency (BATAN) in Indonesia has similar potential. Other potential new producers who are either setting up facilities (e.g. the Egyptian Atomic Energy Authority) or have appropriate facilities and capabilities (e.g. Institute of Atomic Energy in Poland) could be encouraged.

In addition to possible production from its existing appropriate facilities, the Polish Institute of Atomic Energy announced, at a September 2009 workshop in Warsaw organized by the Institute and the IAEA, plans to establish, subject to the outcome of an ongoing feasibility study, a new production facility using LEU targets. The proposed start of operations would be by 2013. Also discussed at the same meeting was the high potential for production capacity in the reactor in Piteşti, Romania.

The ^{99}Mo crisis has increased interest in alternate technologies for the production of ^{99}Mo and their corresponding development issues, specifically:

- photofission of uranium-238 in high power electron accelerators[9];
- aqueous homogeneous reactors[10];
- expanding local and regional use of gel generator technology;
- use of enriched ^{98}Mo targets and neutron activation (thermal and epithermal neutrons) along with the recovery and recycling of the enriched target; and
- use of enriched ^{100}Mo targets by (gamma, n) in high power electron accelerators, (n, 2n) in intense fast neutron sources (e.g. the International Fusion Materials Irradiation Facility) or charged particle induced (p,2n) reactions in medical cyclotrons.

There is also interest in developing additional methods for utilizing (n, gamma) ^{99}Mo, as reflected in work on a high affinity adsorbent for molybdenum in Japan (poly zirconium compound) as well as Australia and India (poly titanium oxochloride), and on an electrochemical separation approach in India. It is possible to obtain (n, gamma) ^{99}Mo of relatively higher specific activity if a higher epithermal neutron flux profile is available in the reactor, since in this case the activation cross-section is nearly 50 times higher. This strategy is being explored at Dimitrovgrad, Russian Federation, which has a reactor with the appropriate features.

There is also the possibility of directly producing ^{99m}Tc by the reaction ^{100}Mo(p,2n), which would take advantage of the very large number of medical cyclotrons (mainly proton accelerators in the 16-19 MeV range) in regular operation around the world and dedicated for medical isotope production. However, yields would be better at proton energies of 20–25 MeV, and, because the natural abundance of ^{100}Mo is only 9.63%, very highly enriched ^{100}Mo targets are necessary for ensuring adequate radionuclide purity of ^{99m}Tc to be suitable for medical use. The technology for recovering and recycling enriched ^{100}Mo targets would need to be further developed, and the economics of daily direct production of ^{99m}Tc in the required quantities is not likely to be competitive compared to ^{99}Mo-^{99m}Tc compact generators.

The question of alternatives to ^{99m}Tc has also been considered, for example, use of thallium-201 for myocardial single photon emission computed tomography (SPECT) imaging and fluorine-18 (as sodium fluoride) for bone PET scanning. While these could serve to a limited extent in certain centres, large scale adoption of these products, or other equivalent PET tracers, matching the volume of procedures possible with ^{99m}Tc products will not be practicable, even in developed countries.

Techniques other than those of nuclear medicine are also being considered in terms of comparative advantage. Cardiac studies might be slightly affected by the introduction of computed tomography (CT) angiography, more likely in developed countries. However, in many cases coronary CT angiography might itself raise an additional need for a SPECT scan for a better functional evaluation of possible anomalies detected on the coronary vessels. For the other important application of nuclear medicine in oncology (bone scanning to detect bony metastatic involvement), which is widely used in developing countries, there are no foreseeable alternatives.

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[9] TRIUMF Mo-99 project (http://www.triumf.ca/home/news-publications/medical-isotopes).
[10] http://www.iaea.org/OurWork/ST/NE/NEFW/rrg_Mo99.html

D. Uranium-235 targets: HEU and LEU

Strategies to increase the reliability of ^{99}Mo supplies must also take into account international efforts to shift from HEU to LEU to strengthen nuclear security. Currently, over 95% of ^{99}Mo production uses HEU targets. About 40–50 kg of HEU per year is used, with less than 5% of the original ^{235}U in the targets consumed during irradiation. Thus a large amount of HEU is left behind in the waste. A 2007 meeting in Sydney under the auspices of the Global Initiative to Combat Nuclear Terrorism detailed the technical and economic aspects and requirements for converting to LEU targets and concluded the following.

- There are no scientific barriers to the production of ^{99}Mo using LEU; small to medium scale production has already been demonstrated.
- The challenge is to move beyond the demonstration of the technical feasibility of the LEU target process to the commercial demonstration of a regular large scale production capability.
- Converting HEU ^{99}Mo facilities to LEU ^{99}Mo requires long lead times and resources. Conversion could take eight years or more.
- Adoption of the LEU process by new entrants to the business ('greenfields') and the conversion of existing facilities using the HEU process ('brownfields') will involve different pathways and needs.

In 2009, the National Research Council of the National Academies in the USA published a report on the feasibility of procuring supplies of medical isotopes from commercial sources that do not use HEU.[11] The report contains a detailed comprehensive account of all the issues and is expected to have a significant effect on strategies for producing ^{99}Mo in the future. It includes specific recommendations to the US Congress, such as cost sharing for conversion related R&D, a 7–10 year phase-out of HEU exports, and continuing government assistance to improve ^{99}Mo supply reliability.

In 2009 national authorities in the USA and Canada approved the use of ^{99}Mo produced by LEU fission, for example by the OPAL reactor, as an active pharmaceutical ingredient. This is an important milestone in the adoption of LEU-based ^{99}Mo for regular use not only in these two countries but also for other generator production centres around the world.

In June 2009, the conversion of Safari-1's core to LEU fuel was completed. Nuclear Technology Products (NTP), working with Safari-1, reported considerable progress on converting targets to LEU. This is the first concrete step towards LEU target conversion by a major ^{99}Mo producer. A number of challenges still need to be addressed, but conversion should be simpler in this case since Safari-1 uses ^{235}U targets that are enriched only up to 46%, compared to 93% targets used by other producers. The conversion to LEU targets is expected to reduce Safari-1's ^{99}Mo production capacity by about 20%.

E. IAEA activities and findings from recent meetings

The IAEA has been involved for more than three decades in fostering developments in ^{99}Mo-^{99m}Tc generator systems. It has coordinated a number of CRPs, with one currently underway on the production of ^{99}Mo using LEU targets or neutron activation. It arranges expert reviews through technical and consultancy meetings, and it publishes technical documents. Examples are

- IAEA-TECDOC-515, *Fission Molybdenum for Medical Use* (1989),
- IAEA-TECDOC-852, *Alternative technologies for $^{99}Tc^{m}$ generators* (1995),
- IAEA-TECDOC-1051, *Management of radioactive waste from ^{99}Mo production* (1998),
- IAEA-TECDOC-1065, *Production technologies for molybdenum-99 and technetium-99m* (1999),

[11] The executive summary is available at http://www.nationalacademies.org/.

- IAEA-TECDOC-1601, *Homogeneous Aqueous Solution Nuclear Reactors for the Production of Mo-99 and other Short Lived Radioisotopes* (2008),
- IAEA-TECDOC-1625, *Research Reactor Modernization and Refurbishment* (2010), and
- IAEA Nuclear Energy Series No. NP-T-5.4, *Optimization of Research Reactor Availability and Reliability: Recommended Practices* (2008).

The IAEA has also supported interested Member States in establishing and/or operating ^{99m}Tc generator production facilities, for example in Bangladesh, China, Indonesia, Iran, Pakistan and Syrian Arab Republic. The IAEA supports the effective operation and utilization of research reactors, which include tasks related to irradiation services and isotope production. The IAEA also fosters coalitions of research reactor operators and users to improve utilization of their facilities, and a topic of interest for coalition members is isotope production as a possible business opportunity. IAEA support for strengthening operational performance of research reactors is also aimed at enhancing the reliability of radioisotope supplies in general and ^{99}Mo in particular.

The IAEA has a number of activities underway to foster the use of LEU targets as well as to help identify and expand the number of reactors engaged in the production of ^{99}Mo. These include the CRP cited earlier on 'Developing techniques for small scale indigenous ^{99}Mo production using LEU fission or neutron activation'[12], encouraging potential facilities to become actual producers (e.g. Egypt), and the establishment of research reactor coalitions to expand and strengthen networks of reactors capable of providing irradiation services (e.g. Poland and Romania). The CRP involves several countries with the potential to become small to medium scale ^{99}Mo producers using LEU targets. Some have made important progress, for example Egypt and Pakistan, on setting up processing facilities. Others have advanced plans, for example Poland and Romania. Egypt and Pakistan are also setting up full-fledged facilities to produce ^{99}Mo based on LEU fission with assistance from INVAP of Argentina and from Isotope Technologies – Dresden of Germany, respectively. Hot commissioning runs are taking place through the first quarter of 2010 in Egypt, and the envisaged capacity is 250 6-day Ci per week.

The IAEA is also reviewing additional production options together with key stakeholders and encouraging potential partnership proposals. One approach under consideration is to provide irradiation services in existing research reactors with suitable features, facilities and operational cycles, and then transport the irradiated HEU targets to existing processing facilities. Obtaining approvals from national authorities for transporting the irradiated targets will be crucial for the success of this approach. Moreover, reactor operators will need to be assured that there will be a continuing reliable demand to justify making the investments to provide such irradiation services. Three specific arrangements to meet immediate and medium term needs are being pursued as follows:

- Covidien, Petten-NL with MARIA reactor of the Institute of Atomic Energy, Poland (begun in March 2010)
- IRE, Fleurus, Belgium with FRM-II reactor of the Technical University Munich (TUM), Germany (target: by 2013)
- IRE, Fleurus, Belgium with LVR-15 reactor of the Nuclear Research Institute Řež, Czech Republic (begun in May 2010)

With IAEA support, the Eurasia Research Reactor Coalition has been established incorporating four reactors in Central Asia and Eastern Europe and one processing facility in Hungary (see FIG. VII-3). It is considering collaborative plans for producing ^{99}Mo using neutron activation of enriched ^{98}Mo targets and, by the third quarter of 2010, aims to increase ^{99}Mo supplies for ^{99m}Tc generators with capacities up to about 0.4 Ci (15 GBq); higher capacity generators will also be feasible after blending with fission-produced molybdenum.[13]

Much of the emphasis in recent studies and meetings triggered by the disruption in ^{99}Mo supplies is on the economics of the front end of the fission-based ^{99}Mo-^{99m}Tc supply chain. The reactor services are not adequately compensated for their support to ^{99}Mo production. High costs for new reactors and for

[12] More details are available at http://www.iaea.org/OurWork/ST/NE/NEFW/rrg_Mo99.html.

[13] More information can be found at http://www.iaea.org/OurWork/ST/NE/NEFW/rrg_EARRC.html.

new ^{99}Mo processing facilities, low margins and the added risk of occasional transport delays and denials all discourage investment. Even for an existing reactor with potential additional capacity, the business case for using that potential is unclear.

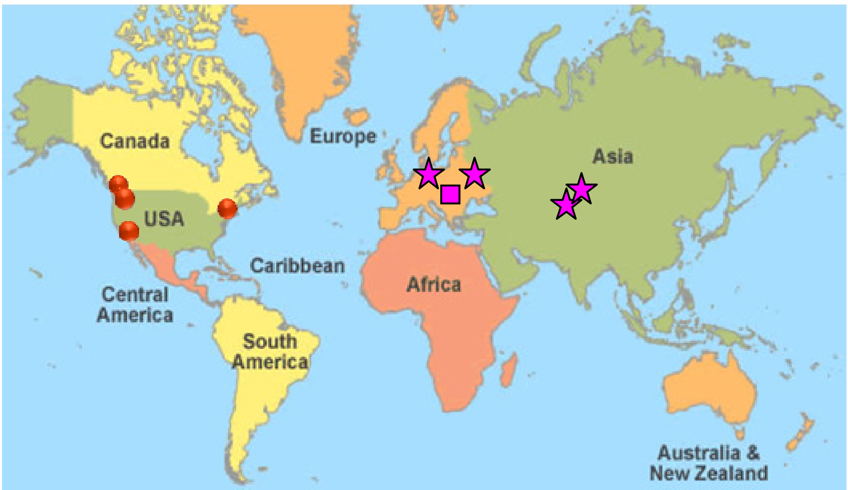

FIG. VII-3: Geographical distribution of Eurasia Research Reactor Coalition: four research reactors in Czech Republic, Kazakhstan, Ukraine and Uzbekistan (stars), an isotope processing facility in Hungary (square) and a number of partners in the USA (spheres).

One possibility is to look to the ^{99m}Tc generator production industry as a potential source of investment in ^{99}Mo production facilities given their existing role in the ^{99}Mo-^{99m}Tc supply chain and special interest in reliable ^{99}Mo supplies. A second possibility arises from the fact that the cost of ^{99}Mo is only a fraction of the ^{99m}Tc generator cost, and even less when compared to the cost of the final radiopharmaceutical dose to be administered to the patient. This implies that a needs-based increase in the price of ^{99}Mo should not have a major impact on the cost of patient services. The US National Academies' report cited earlier includes some analysis of this issue and comments on the economics of ^{99m}Tc dose as follows (recognizing that the study is from a US perspective): "A 10 percent increase in the cost of the ^{99}Mo that is used to produce the ^{99m}Tc doses would translate to about a 0.1 percent increase in the prices of patient procedures. A 10 percent increase in the price of a ^{99m}Tc dose itself would only translate to about a 0.4 percent increase in patient procedure prices." In other words, even if the ^{99}Mo price were to be considerably increased, the net effect on the final cost of the ^{99m}Tc dose should only be marginal. The reality of commercial requirements and practices at different stages of the production chain may, however, lead to a much higher increase than indicated in the US report.

One additional study to be completed during the first quarter of 2010 is an economic analysis of the ^{99}Mo-^{99m}Tc supply chain by the new OECD/NEA High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) that was mentioned earlier. Among other things, HLG-MR is expected to assess the future demands for ^{99}Mo, and address the disincentives created by transport related issues, namely shipment delays and denials and lack of mutual recognition of container licenses. The IAEA's assistance is sought to facilitate harmonized licensing procedures, mutual recognition of container licenses, and ground transport of irradiated uranium targets from reactor sites to existing processing facilities.

F. Concluding remarks

The ^{99}Mo supply chain will continue to remain fragile as long as it continues to rely on the same five aged production reactors. Given the way the supply chain has evolved — particularly its reliance on only five multipurpose, non-commercial, government supported research reactors — there are no clear market incentives to prompt new capacity or alternative supplies. Yet all agree that reliable supplies of ^{99}Mo for medical procedures are essential. ^{99}Mo supply challenges since 2008 have led to the initiation and/or acceleration of multiple ^{99}Mo production projects. Completion of some of these, for meeting supply needs in the near future, will require HEU targets to be irradiated in more reactors and transported along new routes and over greater distances than is currently the case. Coordinated interventions and support by governments are therefore necessary to both ensure the reliability and long term sustainability of ^{99}Mo supply as well as to achieve international, non-proliferation goals related to the minimization of HEU use in civilian applications.

Although any direct IAEA contributions to increased production will necessarily be very limited, the IAEA will continue to help coordinate deliberations and promote joint action to the full extent of its capabilities, in close coordination with OECD/NEA and EC initiatives.

BIBLIOGRAPHY

AIPES Report on Molybdenum-99 Production for Nuclear Medicine 2010-2020. www.aipes-eeig.org; http://www.aipes-eeig.org/index.php?id=57. November (2008).

Bonet, H., David, B., Ponsard, B., Production of ^{99}Mo in Europe: Status and Perspectives, in 9th Intnl Topical Meeting on Research Reactor Fuel Management (RRFM), Hungary. http://www.euronuclaer.org/pdf/RRFM2005.Session1.pdf (2005).

Eckelman, W.C., Coursey, B.M., Eds., Special Issue on '^{99m}Tc Generators, Chemistry and Preparation of Radiopharmaceuticals', Int. J. Appl. Radiat. Isot. 33(10) (1982).

GICNT Workshop Report on the Production of ^{99}Mo using LEU, NNSA and ANSTO, Sydney. December (2007).

Goldman, I., Ramamoorthy, N., Adelfang, P., The IAEA Coordinated Research Project: Production of ^{99}Mo using LEU Fission or Neutron Activation in International Progress Report RERTR Meeting. http://www.rertr.anl.gov/ (2005 to 2009).

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Fission molybdenum for medical use, IAEA-TECDOC-515 (1989).

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Alternate technologies for ^{99m}Tc generators, IAEA-TECDOC-852 (1995).

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Management of waste from ^{99}Mo production, IAEA-TECDOC-1051 (1998).

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Production technologies for ^{99}Mo and ^{99m}Tc, IAEA-TECDOC-1065 (1999).

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Homogeneous Aqueous Solution Nuclear Reactors for the Production of ^{99}Mo and other Short Lived Radioisotopes, IAEA-TECDOC-1601 (2008).

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Research Reactor Modernization and Refurbishment, IAEA-TECDOC-1625 (2008).

INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Optimization of Research Reactor Availability and Reliability: Recommended Practices, Nuclear Energy Series Report NP-T-5.4, IAEA, Vienna (2008).

NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES. *Medical Isotope Production without Highly Enriched Uranium*, The National Academies Press, Washington, D.C. http://www.nap.edu/catalog.php?record_id=12569. January (2009).

OECD-NEA Workshop on Security of Supplies of Medical Radioisotopes, Chair's Summary, Paris. www.nea.fr/html/ndd/RadioisotopesWorkshopSummary.html. January (2009).

Ramamoorthy, N., Production and availability of ^{99m}Tc generators and of ^{99}Mo: Technology considerations and the IAEA contributions in Proceedings of DAE-BRNS Symposium NUCAR-2007, BARC, Mumbai (2007) 24-32.

Ramamoorthy, N., Editorial Commentary: Supplies of Molybdenum-99: Need for sustainable strategies and enhanced international cooperation, Nuclear Medicine Communications 30 (2009) 899-905.

Reports and results of work done under the IAEA CRP in the web site at: http://www.iaea.org/OurWork/ST/NE/NEFW/rrg_Mo99.html.

Ruth, T., Accelerating production of medical isotopes, Opinion Column, Nature 457, (2009) 536-537.

Saraswathy, P., Sarkar, S.K., et al., International RERTR Meeting Proceedings. http://www.rertr.anl.gov/RERTR29/PDF/9-5_Saraswathy.pdf. (2007).

Vandegrift, G.F., Facts and Myths concerning ^{99}Mo Production with HEU and LEU Targets, in International RERTR Meeting. http://www.rertr.anl.gov/RERTR27/Abstracts/S8-1_VandeGrift.html (2005).

von Hippel, F.N., Kahn, L.H., Feasibility of estimating the use of HEU in the production of medical radioisotopes, Science and Global Security, 14, (2006) 151-162.