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The world is currently suffering from a severe shortage of ^{99}Mo and various efforts have been given for its availability. The (n,γ) method is one of candidates for the alternative supply of ^{99}Mo.

The only but critical shortage of (n,γ)^{99}Mo is its extremely low specific activity, which gives inconveniency in the extraction of ^{99m}Tc and is consequently converted to additional cost. Potential technologies which make the (n,γ)^{99}Mo competitive by reducing the additional cost are already available. It is expected that verification of such technologies is much easy and cost effective compared to any other options known for the alternative ^{99}Mo production. Because Japan and Korea import all ^{99}Mo from long distance, the cost benefit of local (n,γ)^{99}Mo production in these countries is especially large. If five high flux reactors in China, Japan and Korea are utilized for the cross backup supply of (n,γ)^{99}Mo, stable availability of ^{99}Mo in the region can be secured. Therefore, it is necessary to evaluate its feasibility on (n,γ)^{99}Mo production in the Asia region.

In this report, we studied feasibility of the mass (n,γ)^{99}Mo production from viewpoints of global and regional status of ^{99}Mo demand and supply, competitiveness with other production methods, requirements and flow of the ^{99}Mo, production capability, cost, convenience in usage, and alternative technologies to overcome its shortage.

Keywords: ^{99}Mo, ^{99m}Tc, (n,gamma) Method, Fission Mo, Generator, MEK, PZC, ALSUL,
Research Reactor, Medical Diagnosis

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(n, γ)法による ^{99}Mo 大量製造に関する研究

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現在、世界において医療診断用 ^{99}Mo は不足しており、^{99}Mo 製造のためのいろいろな努力がその有効性のために行われている。(n, γ)方法による ^{99}Mo 製造は、その供給方法の候補のうちの 1 つである。

(n, γ)^{99}Mo 方法は重大な不足を解決する唯一の方法であるが、^{99m}Tc の抽出において追加費用が必要だけでなく、比放射能が低い。一方、(n, γ)^{99}Mo 方法の追加費用を減らすための技術はすでに利用できる。この技術は他の ^{99}Mo 製造と比較しても非常に簡単で費用効果が良いと予想されている。特に、日本と韓国では、すべての ^{99}Mo を遠隔地から輸入していたが、(n, γ)^{99}Mo 方法による製造コストは近隣諸国での利用により利益は特に大きくなる。もし、中国、日本と韓国にある 5 基の高いフラックスを持つ試験研究炉が(n, γ)^{99}Mo の供給のために利用されるならば、アジア地域における ^{99}Mo の安定供給は確保される。このため、アジア地域における(n, γ)^{99}Mo 製造の実現性を評価することとはに必要不可欠である。

本報告書は、^{99}Mo の需要と供給、他の製造方法に対する競争力及び ^{99}Mo の生産能力、コスト、使用の便宜、その不足を克服するための技術などの必要条件における世界的かつ地域的現状の観点から、(n, γ)による ^{99}Mo 大量製造の実現性について研究した。

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1. Introduction

The ^{99}Mo is the precursor of ^{99m}Tc which is the most widely used tracer for medical diagnoses. Section 2 revisits why the ^{99m}Tc is the best among all isotopes ever found for majority applications of single photon emission computed tomography (SPECT). As explained in Section 3, the procedures to use the ^{99m}Tc are well established in convenient ways, and the burden of ^{99}Mo is sufficiently light in the payment of a patient. Therefore, the ^{99}Mo became one of essential ingredients for medical welfare in modern society, and its global demand is expected to increase during the next decade.

Since timely diagnoses are crucial for most patients who need the ^{99m}Tc, the ^{99}Mo supply has to be continued very stably. However, the world is suffering from a severe shortage in its supply, as explained in appended Section A.1. The worse is that the situation would not be improved within few years. Furthermore, the future would not be much better than before as far as the world depends on a few primary reactors producing ^{99}Mo even they are replaced by new ones, because the fission Mo has inherent risk to the stable availability of ^{99}Mo as explained in Section 3.2. Rather recently, when top two reactors encountered respective long term outages, Canadian and Dutch governments put higher priority on the continued availability of the ^{99}Mo rather than their usual nuclear regulatory practices.

Highly enriched uranium (HEU) targets have been used for the ^{99}Mo production at every primary reactor with risk of nuclear proliferation. International effort to convert the HEU targets to LEU (low enriched uranium) has not been effective in fission Mo production. The USA has supplied the HEU at a lower unit price of ^{235}U than the LEU [1]. The fact that USA consums about a half of global ^{99}Mo all produced at reactors and facilities outside of USA would be one of reasons that they have kept the lower unit price of ^{235}U for HEU.

There are many reactors over the world capable to produce the ^{99}Mo. Should the ^{99}Mo production be shared by many reactors, the risk on the shortage can be significantly reduced. However, the production of fission Mo at many reactors is difficult as explained in Section 4.2, which causes inherent risk to the stable availability of ^{99}Mo.

Section 4.4 explains several efforts to provide additional sources of ^{99}Mo. It is found that readily available facilities are very limited, all other additional productions take time, and new production methods are not fully proven. The $(n,\gamma)^{99}$Mo is one of the alternatives but it is not new technology. It has been used from the initial era of medical ^{99m}Tc applications and it clearly has many advantages compared to the fission Mo. The only one but critical deficiency of $(n,\gamma)^{99}$Mo is the extremely low specific activity, which makes the ^{99m}Tc extraction inconvenient and costly, compared to the fission Mo. Appended Section A.4 reviews the ^{99m}Tc extraction methods to figure out whether the mass $(n,\gamma)^{99}$Mo production has feasibility to be adopted by users who have been using the fission Mo. There are newly emerging generator technologies which significantly reduce the gap in the ^{99m}Tc extraction between fission Mo and $(n,\gamma)^{99}$Mo.

The (n,γ)^{99}Mo has an additional room to compensate its deficiency. The relatively low cost and low safety concern for the (n,γ)^{99}Mo irradiation and post processing are expected to encourage many high flux reactor centers over the world or at least in the East Asian region to join the (n,γ)^{99}Mo production. Then regional rather than global supply schemes are possible, which not only eliminates the risk on the stable availability but also makes the delivery time short and thereby reduces ^{99}Mo cost at the user end. Section 3 explains the difference in the flow of ^{99}Mo between fission and (n,γ), and suggests a scheme for the mass supply of (n,γ)^{99}Mo. Section 5 demonstrates that a high flux reactor can produce a large amount of (n,γ)^{99}Mo for the regional supply.

2. Role of ^{99}Mo in medical diagnoses

The ^{99}Mo is the precursor of ^{99m}Tc which is one of tracers used for medical diagnoses. Since the first tracer study by George C. de Hevesy [2] in 1923 using ^{211}Pb, radioisotopes have been utilized to trace various biologic processes. Generation of ^{99m}Tc from ^{99}Mo was discovered at Brookhaven National Laboratory (BNL) of USA in 1957 and the use of ^{99m}Tc as a medical tracer was first suggested by a Brookhaven scientist Powell Richards [3] in June 1960. After then, development of ^{99}Mo/^{99m}Tc generators and cold kits for ^{99m}Tc labeled compounds led a rapid growth of nuclear imaging for the medical diagnoses.

From various sources, it is roughly estimated that more than 10,000 hospitals over the world use the ^{99m}Tc for about 30 million medical diagnostic procedures every year, which shares about 80 % of nuclear medicine procedures. Demand of ^{99}Mo over the world is some more than 10,000 six-day-Ci (activity in Ci six days after shipment of ^{99}Mo solution) every week, and a few percent growth in annual demand over the next decade is expected. A positron emission tomography combined with computed tomography (PET/CT) gives better diagnostic images than the SPECT using the ^{99m}Tc. But it is much expensive and, due to short half-lives of PET isotopes, it is usually available to hospitals only within about 2 h distance from a medical cyclotron. Moreover, the quality of SPECT images have been improved by advances in detector technologies and reconstruction algorithms together with improved technetium radiopharmaceuticals. The introduction of SPECT/CT has reduced the gap with the PET/CT [4].

Among transmission imaging technologies to obtain structural information by X-ray, ultrasonics and MRI, X-ray is the oldest but its technology has been improved and it is still one of important tools in the modern hospitals. The use of ^{99m}Tc seems a similar case. ^{99m}Tc medicines for targeted imaging were introduced in the mid-1960s, when the MRI, CT and ultrasonography were not available. The ^{99m}Tc is not the first tracer for medical diagnoses, but became most popular among tracers to obtain physiologic information and its technology has been improved as aforementioned. Several nonradioactive tracer techniques as well as PET have been developed, but the application of ^{99m}Tc has been expanded.

In general, the ^{99m}Tc demand is sensitive on the living standard and a chance to be diagnosed by the ^{99m}Tc increases with age. Therefore, rapid development of several countries heavily populated and increase of average age over the world indicate a potential to increase its demand.

The ^{99m}Tc has ideal characteristics for nuclear imaging both in radiation and chemistry as discussed in many references including an IAEA Technical Report [4]. Why it is ideal from the viewpoint of radiation can be understood from relevant radioactive decay data shown in Table 1. Radioactive decay data tables published by DOE in 1981 [5] has been popularly referred in many documents dealing with the ^{99m}Tc, but it is rather old. Table 1 presents the DOE data as well as recently found data from LNHB (Laboratoire National Henri Becquerel) homepage [6].

Every ^{99m}Tc used for the medical diagnosis is produced from the decay of ^{99}Mo. Nuclear reactions producing the ^{99m}Tc directly exist, but the 6 h half-life of ^{99m}Tc not only limits its use within short distance from the production machine but also requires daily production and delivery. There has been no ^{99m}Tc producing machine capable to compete with devices extracting the ^{99m}Tc from the ^{99}Mo. Especially, ^{99m}Tc generators are very convenient to be used by hospitals and radiopharmacies. The 66 h half-life of ^{99}Mo is not long enough for a sufficiently long term use, but the stable weekly production of ^{99}Mo allows the stable availability of ^{99m}Tc. The ^{99}Mo decays to the ^{99m}Tc with 87.6% probability or to the ^{99}Tc with remaining probability. Technologies to obtain the high purity ^{99m}Tc solution from the Mo in convenient and cost effective ways are available.

The ^{99m}Tc is a metastable isomer of ^{99}Tc at an energy level 142.683 keV. Its majority falls to 140.511 keV level by internal conversion (IC) which emits an IC electron and X-ray. Then immediately (0.221 ns) falls to ground level by isomeric transition (IT) emitting a 140.511 keV γ-ray or by IC emitting a corresponding electron and X-ray. The decay process involves M and N shell electrons, making the metastable nucleus susceptible to chemical influences, which gives observable half-life changes from chemical environment. Since the change is sufficiently small, however, it can be neglected in the usual analyses.

The probability emitting the 140.511 keV γ-ray which is used for the imaging is 88.5% in the ^{99m}Tc decay process. Its decay mode is usually called IT, but it is actually composed of above mentioned IC and IT with very low probability β^- decay to ^{99}Ru. The ^{99}Tc decays to ^{99}Ru by emitting a weak β-ray, but its activity is negligible due to its 2.14E5 y half-life. Therefore, majority of energy in the processes of ^{99m}Tc decay is emitted by the 140.511 keV γ-rays, and remaining are low energy IC electrons, Auger electrons and X-rays. Portions of other γ-rays and β-rays are negligible.

While the 140.511 keV γ-ray is good enough for the medical imaging, radiation impact to normal tissue from above mentioned radiations from the ^{99m}Tc is low. Most of all, it is virtually free from high energy β-rays which, when injected into the body, gives much higher impact to normal tissue than γ-rays. Its short half-life decreases a dose rate quickly, as well.

The ^{99m}Tc is usually tagged to molecules targeting specific receptor sites or metabolic processes. Since the element Tc is located in the center of the periodic table, its chemistry is rich and diverse to make many biologically active molecules. It enables imaging almost all the important organs of the body [7].

Such an excellent combination in good γ-ray energy for the medical imaging, low radiological impact both from characteristics of emitted radiations and half-life, much longer availability than its half-life from its precursor, easy and convenient process to get high purity and high specific activity solution ready for radiopharmacy, good chemical characteristics to make various nuclear medicines, together with reasonable cost to use it, marks the ^{99m}Tc an ideal isotope for medical diagnoses.

The portion of ^{99}Mo price in the cost for a medical diagnostic procedure using the ^{99m}Tc is small as discussed in the appended Section A.3. There are many reactors over the world capable to produce large amount of ^{99}Mo. Then, we may suppose that it is easily available. However, the world has been suffering from the shortage of ^{99}Mo as described in the appended Section A.1. Aging of all primary reactors producing ^{99}Mo is often said as the reason of current shortage. But a root cause is that the world has been depending on only a few reactors. As the number of reactors available is small, the risk of shortage becomes high. However, many other reactors cannot help the shortage problem. Its reason is discussed in the Section 4.2.

3. Flow and usage of ^{99}Mo

3.1 Requirements on the use of ^{99}Mo for medical applications

For the medical applications, the ^{99m}Tc produced by β-decay of ^{99}Mo is chemically separated and a solution of sodium pertechnetate (^{99m}TcO$_4^-$ solution) is obtained. Depending on the purpose of a diagnosis, the ^{99m}TcO$_4^-$ solution itself or a ^{99m}Tc labeled compound made by the ^{99m}TcO$_4^-$ solution with a compound is given to a patient by intravenous or oral administration. Then, the distribution of molecules containing the ^{99m}Tc in the patient's body is obtained by a gamma scanning. The scanning may be repeated to get dynamic images. Since the compound before labeling is not radioactive, it is often called as cold kit. As the compound is designed to carry Tc to specific receptor sites or metabolic processes, the image help us diagnose relevant disease. The compound itself has no other medical value to the patient.

The ^{99m}TcO$_4^-$ solution or ^{99m}Tc labeled compound ready for administration to the patient may be prepared by the hospital itself or by a radiopharmacy. Since every process uses the ^{99m}TcO$_4^-$ solution as a starting material, first of all, it has to satisfy basic quality requirements for it. And then, if it is used for a labeling, it has to satisfy additional requirements specific for each labeling, especially for high labeling efficiency. Of course, the labeled compound has to satisfy specific requirements for itself as well. All the requirements focus good imaging with minimum radiation dose and side effects to the patients.

Table 2 summarizes USP (United State Pharmacopeia) specifications for the injection of $^{99m}TcO_4^-$ solution. As the fission Mo has a potential to be contaminated by fission products, uranium and transuranium elements, the specification on radionuclidic impurity is more specific and stringent than the $(n,\gamma)^{99}Mo$. When the ^{99m}Tc solution is separated by the liquid-liquid extraction using methyl ethyl ketone (MEK, see appended Section A.4.2) from the $(n,\gamma)^{99}Mo$, the content of MEK is limited to 0.1%.

An excessive radionuclidic impurity not only increases dose to patients but also indicates lack of reliability in a process to obtain ^{99}Mo or ^{99m}Tc solution. Impurity contents are specified by relative activities to ^{99m}Tc at the time of administration, and ^{99m}Tc generator suppliers usually limit the validity of eluate within 12 h from elution. Therefore, as a rule of thumb, impurity activities valid until 12 h from elution are also applied.

When the radionuclidic purity is sufficiently high, the radiochemical impurity is determined by the ^{99m}Tc in other chemical forms different from the $^{99m}TcO_4^-$, which may have different chemical behavior as well at the post processes including labeling. An excessive chemical impurity not only interferes with labeling but also indicates lack of stability in the ^{99m}Tc extraction process.

For each labeled compound, the biological contamination, radiochemical purity and radionuclidic purity are basic concerns as well. The radiochemical impurity is determined by the ^{99m}Tc in other chemical forms different from the labeled compound, including remained $^{99m}TcO_4^-$. As the ^{99}Tc competes with the ^{99m}Tc in labeling reactions, excessive portion of ^{99}Tc may result in poor labeling [8], which gives lower radiochemical purity. The radiochemical purity is also degraded by chemical instability of the compound, especially under radiation environment.

Once the $^{99m}TcO_4^-$ solution or the labeled compound is prepared, everything degrades as time goes on for the next step. First of all, the ^{99m}Tc decays out. It reduces available ^{99m}Tc and increases portion of ^{99}Tc competing with the ^{99m}Tc for labeling. The radionuclidic purity decreases because the ^{99m}Tc decays out much faster than impurity radionuclides. As concentration of ^{99m}Tc decreases in its solution, more amounts of chemicals including chemical impurities per ^{99m}Tc activity are included in the labeling process and then injected into the patient. Meanwhile probabilities of biological contamination and of degradation in radiochemical purity increase. Therefore, time intervals from preparation of $^{99m}TcO_4^-$ solution to labeling and to administration are also important specifications. It is usually recommended to minimize the time intervals as possible.

On January 12, 2009, US Nuclear Regulatory Commission (NRC) [9] issued an information notice about an unusual number of reports on failures of ^{99}Mo breakthrough tests. The NRC informed that the majority of the reports involved concentrations of ^{99}Mo that did not exceed the regulatory limit at the time of elution but, due to the decay rate of ^{99m}Tc, the ratio of ^{99}Mo to ^{99m}Tc would have exceeded the regulatory limit before the 12 hours post elution expiration time stated in the generator package insert. AM Millar [10] reported a degradation of radiochemical purity by using the aged eluate (The eluate is $^{99m}TcO_4^-$ solution eluted from the ^{99m}Tc generator).

The time interval between extractions of ^{99m}Tc from a generator also affects to the available ^{99m}Tc activity, and may impact to the quality of $^{99m}TcO_4^-$ solution and labeling efficiency. As explained in appended Section A.2.5, the ^{99m}Tc activity in the Mo reaches a maximum value at 22.84 h and then decreases by approaching a transient equilibrium. The portion of ^{99m}Tc in Tc monotonically decreases until next extraction of ^{99m}Tc. The chemistry of molecules containing ^{99m}Tc degrades with time. Therefore, extraction time interval longer than 24 h gives no benefit. A cold kit supplier [11] limiting the elution interval within 24 h for ^{99m}Tc exametazime was also found.

The amount and activity of eluate for a labeling process depend on the compound. Cold kit suppliers usually specify valid age of eluate, valid life time of each labeled compound, volume and activity of eluate needed for each labeling process, etc. ^{99m}Tc generator suppliers usually specify expiring age of eluate as well.

Figure 1 summarizes above specifications. For the labeling of a compound, the elution time interval (T_E) can be limited within 24 h. ^{99m}Tc generator suppliers usually limit time to administration after elution ($T_L + T_A$) within 12 h. Therefore, a valid age of the eluate (T_L) can be a maximum 12 h when it is administered directly. Therefore, T_L can be in the range 0 ~ 12 h. However, the use of fresh eluate is usually recommended and the age of eluate is limited within short time for the labeling of some compounds.

While some labeled compounds allow administration up to 8 h after labeling, the age of a labeled compound (T_A) should be as short as possible for administration, as well. Therefore, T_A can be in the range 0 ~ 8 h. It is usually recommended to administer labeled compounds whenever they are ready, and some compounds require almost immediate administration.

After administration, usually a few hours are required for imaging unless it is for a dynamic imaging which usually begins soon after administration.

Among all cold kits listed in an IAEA Technical Report [4], the highest ^{99m}Tc activity is for the MDP; 4 mL of freshly eluted $^{99m}TcO_4^-$ solution containing a maximum of 500 mCi of activity. It corresponds to a maximum volumetric activity 125 mCi/cm^3. The maximum activity of ^{99m}Tc administered to a patient is 30 mCi unless a strong justification exists. However, Japanese radiopharmacies operating 500 Ci Master milkers calibrated at 12:00 Friday, require minimum 1 Ci/cm^3 for the activity of eluate just after elution at 09:00 next Friday. It is 8 times of above mentioned maximum activity (125 mCi/cm^3) and equivalent to compensating decays for three half-lives of ^{99m}Tc (18 h). But such decay seems not feasible as the life time of eluate is limited as aforementioned.

R.E. Boyd [12] mentioned that the ^{99m}Tc solution obtained from (n,γ)^{99}Mo/^{99m}Tc jumbo gel generators using zirconium molybdate is too dilute for immediate clinical application and therefore, some form of concentration step is necessary. Though the ^{99m}Tc solution from portable gel generators has a lower ^{99m}Tc concentration than that from jumbo gel generators, however, it does not need the concentration step. The Master milker is the highest activity jumbo generator used by radiopharmacies. Therefore, the processes in radiopharmacies may require much higher ^{99m}Tc concentration than hospitals, but its reason is not clearly disclosed. The requirement may come from its two weeks use because the ^{99m}Tc concentration decreases to about 17% after one week if an identical amount of eluent is used.

3.2 Flow of fission Mo

Virtually all ^{99}Mo used over the world is the fission Mo. As explained in appended Section A.1.2, four companies have shared more than 95% of the world ^{99}Mo supply using five reactors and four post processing facilities. MDS Nordion intended to cover the global demand by alternating operation of two MAPLE reactors. If it was successful, the ^{99}Mo production using the two reactors and one post processing facility of MDS Nordion may be cost effective compared to the current world production involving five reactors and four post processing facilities. Then, the ^{99}Mo production at other new reactors would be difficult to be justified, and the world may become dependent only two MAPLE reactors in the future. Assuming such scenario is possible because very high specific activity of fission Mo in combination with the large production capability of a reactor specifically designed enables global supply of ^{99}Mo from very few facilities.

However, it has risk for the global stable availability of ^{99}Mo. It is said that age of the primary reactors producing ^{99}Mo caused current shortage, but it is a superficial reason. For many years, the world has been depending on the primary reactors with risk not only from unscheduled shut downs of the reactors but also in global transportation of ^{99}Mo. Since top three reactors had shown excellent availability, the risk might be intentionally ignored. However, less aged reactors also have potential to have long term outage. Since long distance transportation of ^{99}Mo becomes impossible when flights are not available due to various reasons, the global supply scheme also has potential to disturb the stable availability of ^{99}Mo. It is especially important to Japan and Korea because they are at long distance from all major suppliers.

When the supply is interrupted, there is almost no alternative to backup. There are many reactors over the world capable to produce the ^{99}Mo. Therefore, if the ^{99}Mo production is shared by many reactors, the risk on the shortage can be significantly reduced. Unfortunately however, the production of fission Mo at many reactors is difficult as explained in Section 4.2. If the MAPLE project was successful, the risk would be higher. As two MAPLEs have exactly identical design features, if a common mode problem shutting both reactors down for long term occurs, virtually no ^{99}Mo will be available over the world. Therefore, as far as the world is depending on the fission Mo for the majority, the risk will remain.

All fission Mo is used for the ^{99m}Tc generators, and there are three prior processes for the use of ^{99m}Tc generators; irradiation of uranium targets, chemical process to recover ^{99}Mo from irradiated targets and loading of ^{99}Mo solution into ^{99m}Tc generators. A lot of ^{99m}Tc generators are made from the Mo solution every week. Since a total weight of all generators for a region consuming many generators is much heavier than the shielding for the transportation of ^{99}Mo solution to the region, long distance transportation of many generators is inefficient. Therefore, many ^{99m}Tc generator loading facilities using the ^{99}Mo from the four major suppliers are distributed over the world.

The flow of fission Mo from the loading of target for irradiation to the use of ^{99m}Tc is shown in Figure 2. When the reactor and facilities for the post processing and the ^{99m}Tc generator loading are located at a same site, generators will be available to nearby area in the shortest time. Unless the post processing facility is directly connected to the reactor, the targets have to be transported using a cask. Since the activity of the targets is very high, the cask is too heavy for the air transport. Therefore, the surface transportation only within reasonable time duration is practical. Two companies in Europe are operating their post processing facilities at HFR and BR2 sites, respectively, and utilize HFR, BR2 and OSIRIS for cross backup irradiation. When they irradiate their targets at reactors of other sites, transportations of irradiated targets to outside of reactor site are needed. Very strict material accounting for safeguard of HEU may not allow sharing of targets between two companies. Anyway, at least several hours are needed for the transportation of irradiated targets including packaging and inspections.

Major ^{99}Mo suppliers may operate generator loading facilities at their reactor sites as well, but a large portion of their production is supplied to several other generator loading facilities over the world. In many countries not producing sufficient ^{99}Mo solution, local companies import the ^{99}Mo solution and make ^{99m}Tc generators for local supplies. When the local market is not sufficient for the operation of a ^{99m}Tc generator loading facility, the ^{99m}Tc generators can be imported.

The ^{99}Mo solution and ^{99m}Tc generators are also sold on the basis of ^{99}Mo activity, but their activity calibration is different as explained in appended Section A.3.2. The activity of ^{99m}Tc generators are usually from less than a half to about 20 Ci on the day of manufacture. Low activity generators called portable generators are usually used at hospitals for in-house procedures. High activity generators called jumbo generators are usually used by radiopharmacies. The radiopharmacies usually buy the jumbo generators from various sources and supply the ^{99m}Tc nuclear medicines ready for administration to many hospitals. For the case of radiopharmacy companies in Japan operating Master milkers, they may have integrated functions - import of ^{99}Mo solution, Master milker loading, and production and distribution of nuclear medicines. Activity of a Master miker is 500 Ci on the day of manufacture, which is exceptionally high.

As discussed in the appended Section A.3, the current global ^{99}Mo supply scheme is not friendly to Japan and Korea. The geographical locations of all major ^{99}Mo production reactors not only make the cost of fission Mo about twice of USA but also give a higher probability of unavailability due to problems in transportation, for the two countries.

3.3 Flow of (n,γ)^{99}Mo

The (n,γ)^{99}Mo had been used at the initial era of ^{99}Mo until the fission Mo became available. It is remained for local supplies to very limited demands. As explained in Sections 4.2 and 4.3, the (n,γ)^{99}Mo has several advantages compared to the fission Mo, but the extremely low specific activity makes its uses less convenient than the fission Mo, which makes majority of users not to choose it as far as the fission Mo is available.

Its use may be through ^{99m}Tc generators or ^{99m}Tc extraction devices as shown in Figures 3 and 4. The distribution of ^{99}Mo solution by the same way as fission Mo in Figure 2 may be possible, but the current use of (n,γ)^{99}Mo is too small for such distribution. Even though its use is significantly increased and backup supply of ^{99}Mo becomes active, transportation of ^{99}Mo solution is not an efficient way. As discussed in the next section, transportation of irradiated targets instead of its solution is much better.

When the generators are involved, the flow becomes the same as fission Mo shown in Figure 2, except that the Mo solution transport path is deleted as in Figure 3. However, only Zr gel generators [13] are currently used for the (n,γ)^{99}Mo in a few countries. As explained in appended Section A.4.3.2, preparation of the Zr gel generator is complex and time consuming. Therefore, its use is limited to small amount of low activity generators. If new adsorbents explained in appended Section A.4.3.3 are successfully verified, use of portable generators based on the (n,γ)^{99}Mo is expected to increase. It also has potential to be used for the jumbo generators by radiopharmacies along the dotted flow in Figure 3, but the large volume of column causes rather large difference compared to the use of fission Mo based generators. Radiopharmacies may compare with the use of the ^{99m}Tc extraction device as Figure 4.

The ^{99m}Tc extraction device in Figure 4 has been based on solvent extraction method explained in appended Section A.4.3.1. It can neither be compact nor convenient compared to usual generators, especially to the user end. Therefore its operation at a hospital is not practical. It has been usually operated by a radioisotope group of a research reactor center to supply small amount of ^{99m}Tc to local hospitals. The short ^{99m}Tc half-life requires daily supply only within short distance. Therefore, such ^{99m}Tc supply scheme cannot be applied to the mass supply. However, the device may be used by a radiopharmacy for the supply of ^{99m}Tc nuclear medicines to many hospitals. It is not as convenient as the use of jumbo generators based on fission Mo. However, as discussed in appended Section A.4, the low cost for the (n,γ)^{99}Mo may provide a large room to compensate the additional cost coming from the inconvenience.

3.4 Potential scheme of mass (n,γ)^{99}Mo supply

As the extremely low specific activity of the (n,γ)^{99}Mo is the only and critical limitation to use it, every reasonable effort should be given to increase the specific activity so as to realize its mass supply. The high specific activity is basically obtained by irradiating targets under high neutron flux. The use of enriched ^{98}Mo instead of natural Mo increases the specific activity as well as the production capability three to four times. In addition, the decay time of ^{99}Mo after end of irradiation has to be minimized.

It may be supposed that if similar efforts are given to the fission Mo, its availability will be enhanced as well. However, it is not such a way. As explained in Section 4.2, the production capability of fission Mo is limited by safe cooling capability and not proportional to the neutron flux at high level. The HEU has been already used for the fission Mo targets in spite of nuclear proliferation risk, and USA has supplied the HEU at a lower ^{235}U unit price than the LEU. Therefore, there is no more room to increase the ^{235}U enrichment. It requires much longer time than the (n,γ)^{99}Mo for target cooling and post processing, which cannot be reduced due to safety of targets. Expensive facilities for the target irradiation in the reactor and post processing, as well as expensive procedures in the post processing can be justified when a significant portion of world demand is shared, which consequently requires global supply and long transportation time.

As explained in Section 4.3, compared to fission Mo, the (n,γ)^{99}Mo requires much simple and less expensive facilities as well as low cost for its production and post processing. And many high flux reactors over the world have large production capability. Therefore, regional supply of (n,γ)^{99}Mo is possible. It not only significantly reduces the risk of global ^{99}Mo unavailability coming from unscheduled outage of reactors and problems in global transportation, but also increases efficiency in the use of ^{99}Mo by reducing decay time.

For the case of fission Mo, the transportation of irradiated targets is difficult due to very high activity. But the transportation of irradiated (n,γ)^{99}Mo targets is easier than the ^{99}Mo solution. After de-canning, activity of irradiated targets is the same with Mo solution. Volume of solid targets is much less than the Mo solution, transportation of solid targets is safer than solution, and there is no safeguard requirement which is applied to fissile materials. When the transportation is to another country for such as backup supply, fewer facilities are involved for the medical license as well. When the targets are dissolved at a foreign facility for the import of the Mo solution, the dissolving activity at the foreign facility may also be involved for the medical license of the country using it.

At least a hot laboratory is available at the site of a high flux reactor, in which the targets can be dissolved. When the ^{99m}Tc generator loading facility is apart from the reactor, however, dissolution of the targets at the ^{99m}Tc generator loading facility after the transportation of irradiated (n,γ)^{99}Mo targets is recommended. It makes the medical license simple and reduces cost and time for the transportation when the (n,γ)^{99}Mo is supplied from abroad for the backup supply. Since the process dissolving de-canned (n,γ)^{99}Mo targets is simple, it may be included into the process of ^{99m}Tc generator loading.

The regional mass (n,γ)^{99}Mo supply scheme especially for the East Asian region is depicted in Figure 5. Then, reactor operators irradiate targets, de-can the targets and ship to companies operating ^{99m}Tc generator loading facilities. The companies may supply ^{99m}Tc generators and/or ^{99m}Tc nuclear medicines to hospitals. When it is compared with the current practice of fission Mo, the company operating post processing facility is missing. Therefore, the companies operating ^{99m}Tc generator loading facilities will make contracts with reactors for the target irradiation including backup.

4. Production of ^{99}Mo

4.1 Nuclear reactions producing ^{99}Mo

Table 3 summarizes nuclear reactions producing ^{99}Mo. Reactions directly producing ^{99m}Tc are not included because directly produced ^{99m}Tc is not feasible for practical medical applications as explained in Section 2. Cost for mass production, convenience in the usage of ^{99m}Tc and technical feasibility govern the selection of a reaction for the actual production.

From the table, it is very clear that the fission reaction of ^{235}U is the first choice. The thermal neutron cross section of ^{235}U producing ^{99}Mo is about 30 b, which is much larger than any other reactions. Specific activity of ^{99}Mo in the recovered Mo from irradiated uranium is very high as explained in appended Section A.4.2. The suggestion of TRIUMF [14] for the use of ^{238}U(γ,f) also have similar justification, but, in addition to the technical challenges, its cost effectiveness must be proved.

From a target other than Mo, the ^{99}Mo produced by the nuclear reactions can be chemically separated from the target material and very high specific activity ^{99}Mo can be obtained. Uranium fissions, ^{99}Tc(n,p), ^{102}Ru(n,α) are such cases. Among them, however, ^{99}Tc(n,p) and ^{102}Ru(n,α) are threshold reactions of fast neutrons with very small cross sections. Therefore, they are not feasible for a practical production of ^{99}Mo. The ^{99}Tc is one of candidates for burning by nuclear transmutation to reduce long term toxicity of spent fuel. If fast reactors burning ^{99}Tc become available, the ^{99}Tc(n,p) may be considered for the ^{99}Mo production as a byproduct but its justification may not be easy due to the low cross section.

Every reaction with a Mo isotope target has a common shortage of low specific activity unless the ^{99}Mo is separated from the target material by a special method. When the ^{99}Mo cannot be separated by a practical way, the specific activity can be increased only by increasing incident beam intensity, which is always very costly and has limitation.

In the table, the cross section of ^{98}Mo(n,γ) is much less than ^{100}Mo(n,2n), but, since it is thermal neutron reaction, it has been utilized for small scale local supplies of ^{99}Mo using research reactors. As shown in Figure 6, the ^{98}Mo(n,γ) also has many resonance capture peaks in the epithermal energy region, of which ratio to the thermal neutron cross sections is much higher than the ^{235}U.

The ^{100}Mo(n,2n) has relatively high cross section 1.5 b for 12 ~ 17 MeV energy neutrons. Yasuki Nagai and Yuichi Hatsukawa [15] suggested this reaction together with accelerator based high energy neutron sources as a potential way of ^{99}Mo production. They supposed that the suggested method would have comparable production capability and specific activity as the ^{98}Mo(n,γ) method in the research reactors. Its feasibility for an actual ^{99}Mo production may be considered when it can give high specific activity at reasonable cost compared with the ^{98}Mo(n,γ) method.

They also mentioned about ^{100}Mo(p,pn) and ^{100}Mo(γ,n) including some reactions directly producing ^{99m}Tc that their yield is low. Ralph G. Bennett et al. [16] got a patent including a method irradiating photons to ^{100}Mo targets in 1998. Aforementioned low yield would be one of reasons that ^{100}Mo(γ,n) and ^{100}Mo(γ,p) has not been in practical use yet. They also mentioned that an approach to utilize ^{100}Mo(p,d) reaction generated various side reactions which adversely affected product purity tests. The cross sections of ^{98}Mo(d,p) is too low to take into account.

4.2 Fission Mo

The fission method gives a mass production of very high specific activity ^{99}Mo, and ^{235}U(n,f)^{99}Mo shares all ^{99}Mo supplied over the world except minor local supply of (n,γ)^{99}Mo. A fission produces 200 MeV energy in average and a ^{99}Mo nucleus with 6.17% probability. Therefore, a fission power from targets necessary for the world supply of ^{99}Mo can be easily guessed with following assumptions; the target is irradiated 6.5 days, 2 days are needed for target cooling and post processing, an efficiency of the post processing is 90%, the ^{99}Mo activity is calibrated after 6 days from the shipping after the post processing, and the world demand is about 10,000 six-day-Ci/w. Then about 2 MW fission power is needed for the world ^{99}Mo supply, which is similar with the power from one or two fuel assemblies of typical high flux reactors.

From above, we can imagine that if a high power research reactor is operated for the fission Mo production with a high priority, the reactor can have a peak production capacity to cover a large portion of the world demand. In addition to the very high specific activity which allows long distance transportation, it enables very few reactors to cover majority of the world demand.

The most limiting factor determining the production capability of fission Mo is a safe level of power generation from a target. The loading of ^{235}U in an irradiation hole is limited within the capability of safe cooling of targets not only during irradiation but also after end of irradiation. During irradiation, the fission heat from targets must be sufficiently cooled by the same way as the fuel cooling. When the targets are withdrawn from the neutron flux region after end of irradiation, they should be under continued forced cooling until natural cooling in the water becomes sufficiently safe. Then they should be under the water until the cooling in the hot cell atmosphere or transport cask becomes sufficiently safe. However, the cooling time has to be reasonably short to prevent excessive decay of ^{99}Mo. Since the decay heat is proportional to the fission power during irradiation, in order to keep the reasonable cooling time, the heat generation from the target during irradiation should also be limited.

When the neutron flux is very high, the uranium loading must be reduced so as to keep the heat generation below a safe limit. In contrary, when the neutron flux is low, the production capability can be increased by high uranium loading, but it significantly increases neutron self shielding due to the large absorption cross section of ^{235}U. Of course, the production cost is high because of not only the cost for the high uranium loading but also a large amount of waste produced from the target containing large amount of uranium.

As shown in Figure 6, the ^{235}U fission cross section of thermal neutron is much larger than those of epithermal and fast neutrons, and actually majority of fission reactions are occurred by thermal neutrons under the usual research reactor neutron spectrum. Therefore, irradiation holes in the reflector region of a research reactor providing a high thermal neutron flux can be effectively utilized for the fission Mo production. An example is the preliminary design of LEU target irradiation at MURR [17]: Loading of 60 g ^{235}U could supply 50 % US market by repeating 3 days irradiations twice in a week. Their calculation resulted in 133.3 Ci-^{99}Mo/g-^{235}U at the end of 3 days irradiation.

The fission produces other valuable isotopes such as ^{131}I, ^{89}Sr, ^{133}Xe and ^{90}Y for medical applications, and other long lived isotopes for industrial applications. Therefore, the production of fission Mo offers a possibility for coproduction. Since the coproduction is limited to short lived isotopes due to short irradiation time, ^{90}Y and long lived isotopes for industrial applications cannot be included. The half-life of ^{90}Y ($t_{1/2}$ = 64 h) is not so long, but carrier free ^{90}Y ($t_{1/2}$ = 64 h) is produced from decay of ^{90}Sr ($t_{1/2}$ = 28.8 y). The long half-life of ^{90}Sr does not give sufficient activity of ^{90}Sr by the weekly irradiation of fission Mo targets. For the production of long half-life fission products, by products from the reprocessing process of spent fuel would be much better.

It seems that the ^{131}I ($t_{1/2}$ = 8 d) is the major byproduct from the fission Mo targets. However, mass production of high specific activity ^{131}I can also be achieved by ^{130}Te(n,γ)^{131}Te reactions followed by β^--decay of ^{131}Te ($t_{1/2}$ = 25 m). Cross sections of ^{130}Te(n,γ) are similar level as the ^{98}Mo(n,γ). ^{133}Xe ($t_{1/2}$ = 5 d) may also be produced by ^{132}Xe(n,γ) reactions, but it would not be practical compared to the extraction from the off gas of fission Mo targets. While ^{89}Sr ($t_{1/2}$ = 50.5 d) has been produced by ^{89}Y(n,p) or ^{88}Sr(n,γ) reactions, a patent [18] obtaining it from a solution fueled reactor was issued. Anyhow, the capability to produce other isotopes is an additional advantage of the fission Mo method.

Meanwhile the fission Mo has well known problems. Irradiation and post processing facilities are safety sensitive and much expensive, the post process is complicated with risk of fission gas release and produces much radwaste, and the use of HEU has nuclear proliferation risk.

The current world situation suffering from the shortage of ^{99}Mo reveals the problems very evidently. There are many high flux reactors capable to produce a large amount of fission Mo, but they are practically not helpful to the shortage. Most of all, the installation of new facilities is not only safety sensitive and expensive, but also requires long time for licensing. In contrary, income from the operation of the facilities is doubtful unless a significant portion of world supply is shared. The post processing facility should be available within reasonable distance because air transportation of irradiated targets is impractical. A few reactors in Europe are free from the burden installing a new post processing facility, but only MARIA was additionally available when HFR was shutdown in February 2010.

Majority of fission Mo is produced from HEU targets, but the HEU is not available to new fission Mo producers, due to the nuclear non-proliferation policy. It is usually said that waste shares the largest portion in the cost of fission Mo production. Since the use of LEU produces more amount of waste, new producers are less competitive than existing suppliers. Furthermore, there is no guarantee that they can maintain a certain scale of business when the current shortage problem is resolved. No major supplier of ^{99}Mo has converted to LEU yet. Conversion of existing facilities to process LEU includes not only change of the facilities but also new medical licenses for the use of ^{99}Mo, which has been one of reasons that the major suppliers have not converted to LEU. The new producer should get the medical license as well not only for the use of LEU but also for all of their processes.

Russia produces fission Mo using HEU, but their product is not used in other countries yet. They may need to expand their hot cell facilities for the additional production. The ^{99}Mo produced by LEU targets at OPAL got license for the use of their ^{99}Mo solution in USA. It may encourage RSG-GAS to apply a new license for the ^{99}Mo production using LEU. If they need modification of existing facilities or new hot cell facilities for the expanded supply, however, a few years may be needed to initiate actual mass supply. Therefore, they cannot help the current shortage of ^{99}Mo.

Therefore, it is clears that the root of current problem is expensive facilities for the fission Mo production compared to the business scale, which cannot be justified unless sharing of a continued significant portion of world market is guaranteed.

4.3 $(n,\gamma)^{99}Mo$

The advantage of (n,γ) method compared to the fission method is well known. Facilities for irradiation and post processing for a new production are quite simple and much less-expensive, virtually no waste is produced, the ^{99}Mo solution is free from fission products and actinides, and there is no risk of nuclear proliferation. It may be supposed that the production capacity is low because of the much low $^{98}Mo(n,\gamma)$ cross section compared to ^{235}U fission. However, actual production capability is comparable to fission method as discussed in Section 5.1.

Critical shortage of (n,γ) method is the extremely low specific activity compared to fission Mo, which has limited its utilization only for minor local supplies. As far as an effective separation of ^{99}Mo from the target Mo is not available, the portion of ^{99}Mo in the Mo is a few ppm at the end of irradiation even at high flux reactors. When the ^{99m}Tc is extracted for use, its concentration in the Mo is less than a few percent of above ^{99}Mo concentration – decades of ppb in the total Mo. Separation of the ppb level ^{99m}Tc is not as difficult as enriching an isotope, but it is not an easy task. It is common for every process producing an isotope of different element by neutron capture reactions. For the case of ^{99}Mo, however, extraction of ^{99m}Tc from fission Mo is too convenient to allow competition by the $(n,\gamma)^{99}Mo$.

The importance of the high specific activity of ^{99}Mo as possible comes from the fact that virtually all ^{99}Mo has been used for the ^{99m}Tc generators which are very convenient to use at the user end. As explained in appended Section A.3, thousands of generators are delivered every week, and the portion of cost for the ^{99}Mo production in the payment of patients is very small. Therefore, while the low cost for the $(n,\gamma)^{99}Mo$ production is a minor advantage, the inconveniency in the usage of the low specific activity $(n,\gamma)^{99}Mo$ impacts significantly.

In order to make the ^{99m}Tc generators from the $(n,\gamma)^{99}Mo$, a large volume of generator column is needed due to the low specific activity, which consequently requires increased amount of saline solution for elution and decreases volumetric ^{99m}Tc activity of eluate. It increases generator shielding as well. If the volumetric ^{99m}Tc activity of eluate does not satisfy its requirement, a process to concentrate the eluate is needed or the labeling technologies must be changed. Since this impact cannot be accepted from the hospitals, at least the process at the hospitals should not be so different from the usage of fission Mo. If it is so, other impacts such as increased shielding, more works of radiopharmacies, etc., would be marginal and may be compensated by the low cost for the $(n,\gamma)^{99}Mo$ production.

Then it is clear that the ^{99m}Tc extraction methods discussed in appended Section A.4 are keys determining the acceptance of $(n,\gamma)^{99}Mo$. The solvent extraction method has been used at several research reactor centers for the local supply of ^{99m}Tc solution. This method instead of Master milkers may also be used by the radiopharmacies. Two new adsorbents – PZC [19] and ALSUL [20], open possibility of competitive generators using the $(n,\gamma)^{99}Mo$ to replace portable generators using fission Mo. They may also be used for the jumbo generators including Master milkers, but a detailed study comparing with the solvent extraction method will be needed.

In order to reduce the volume of generator column using (n,γ)^{99}Mo, every effort to increase the specific activity of ^{99}Mo without significant impact to the production capacity should be given. Optimum design of irradiation targets and facility at high neutron flux is basically needed to maximize the specific activity. In addition, efforts should also be given to minimize decay time after irradiation, which is possible because of much simple post processing of (n,γ) targets. Additional possibility to shorten the decay time is to activating regional supply of ^{99}Mo. Should the effectiveness of even only one of the new Mo adsorbents under study is fully verified, the simple and less-expensive (n,γ) method may encourage many high flux reactors to initiate ^{99}Mo production. If so, many high flux reactors over world can contribute to the regional ^{99}Mo supply, which can shorten time for ^{99}Mo transportation.

The regional supply system is important for the stable supply as well. Since much more reactors are producing the ^{99}Mo, the impact from unavailability of a reactor becomes small. As the global transportation of the ^{99}Mo is not needed, the impact coming from unavailability of air transportation becomes smaller as well.

4.4 Approaches for new production

Recent shortage in global supply of ^{99}Mo motivated many efforts to mitigate it. Of course, the quickest way is the improvement of efficiency in the delivery of ^{99}Mo and usage of the ^{99m}Tc. As explained in appended Section A.3.3, the cost of ^{99}Mo for a diagnostic procedure using ^{99m}Tc has been small portion in the payment of the patient, which has led the convenience to be more important than the efficiency in the processes after the ^{99}Mo solution is made. Therefore, there has been room to improve the efficiency. If the processes are optimized, the number of procedures covered by the same amount of ^{99}Mo is estimated more than twice of usual practice before the shortage became serious. As explained in appended Section A.2.5, the availability can be additionally increased by multiple elution of a generator in a day.

Now, in order to utilize the ^{99m}Tc as much as possible, it may be used even during nights and weekends. However, it is still less than demand. Therefore, alternative ^{99}Mo production is urgently needed. The alternatives under progress or study are summarized in appended Section A.1.4. This section categorizes them by additional fission Mo production by conventional way, mass (n,γ)^{99}Mo production, solution fueled reactors and photo fission of ^{238}U, and explains current situation and prospect of each category.

4.4.1 Additional fission Mo production by conventional way

If existing reactors can be utilized to increase fission Mo production, it is the quickest way to alleviate the shortage. It is said that operation schedules of BR2 and OSIRIS are adjusted to minimize the impact from the long term shutdown of the HFR from 19 February 2010, production capability of BR2 was increased, and Maria in Poland initiated to irradiate fission Mo targets. Therefore, among many reactors capable to produce fission Mo, actual reactors available for the additional production are very limited.

On June 15, 2009, MDS Nordion agreed to study the feasibility of the Karpov Institute of Russia providing the company supply of ^{99}Mo for the global market, but there has been no news so far that they are actually supplying to the global market. It is also estimated that OPAL has the capacity to produce a half of the world's ^{99}Mo demand, but the capacity of post processing facility is not enough.

Since air transportation of irradiated fission Mo targets is not practical, the production capability of a reactor can be utilized only within the capability of post processing facility available. When a high capacity post processing facility is available, installation of new or additional irradiation facilities in the reactor is needed. However, they are expensive and long time consuming. Therefore, prompt utilization of existing reactors is actually limited to the abovementioned BR2 and Maria. Operation report of Maria in 2006 [21] shows that the reactor was operated by weekly mode — 4 ~ 5 days operation per week. Then, since on-power loading and unloading of fission Mo targets are not necessary, the irradiation facility can be rather simple and the Maria can be immediately utilized for the ^{99}Mo production. It was said that the production will cover about 1M ^{99m}Tc diagnostic procedures during first six months among about 35M/y procedures over the world.

FRM-II is seeking funding to upgrade the facility to produce ^{99}Mo [22]. The study was a cooperative effort between the reactor operator TUM and ^{99}Mo supplier IRE assuming irradiation of IRE targets and post processing at IRE facility, the local and the federal governments recommend unanimously the project, and the TUM will install a new zircaloy thimble to accommodate the fission Mo irradiation facility on its own expense during a long maintenance period at the end of 2010. However, they are still suffering from lack of funding. If the funding is available on time, they estimate the irradiation service from end of 2013 or beginning of 2014. Unless the IRE facility is converted to deal with LEU targets, they must irradiate HEU targets. In such case, they expect almost enough peak ^{99}Mo production capability to supply the demand in Europe.

McMaster University [23] in Canada stated that it can produce four times the Canadian demand for ^{99}Mo (about 20 percent of the total North American demand) provided it receives government funding over the next five years. The university has already received C$22 million from both the federal and Ontario governments. Irradiated targets will be processed at AECL facility.

Missouri University [17] has been studying ^{99}Mo production at MURR using LEU targets and Cintichem process. They expect about 50 % domestic supply from 2012.

JHR is the only new reactor under construction and capable to produce fission Mo in the future. International bidding of PALLAS is pending and MYRRHA is under conceptual design. Canada is thinking about construction of a new 20 MW Canadian Neutron Source. All new reactors except the JHR are still far to produce the ^{99}Mo.

4.4.2 Mass (n,γ)^{99}Mo production

The (n,γ)^{99}Mo has been utilized for small local supply. JAEA and KAERI have studied feasibility of mass (n,γ)^{99}Mo production. This report is one of the results from the studies. On 30 September 2009, two Cooperative Agreements were awarded to commercial partners to accelerate the production of ^{99}Mo in the U.S. without the use of HEU [24]. They are Babcock and Wilcox (B&W) for solution reactor technology which is explained in the next section and General Electric Hitachi (GEH) for (n,γ)^{99}Mo technology. News on 26 January 2010 said that GEH would utilize GE-built commercial reactors in place of a neutron-detecting instrument. Robert Atcher, past president of the Society of Nuclear Medicine, evaluated GEH's isotope technology, and commented that the technical solution provides a path forward that is quite attractive to meet some short-term solutions that have long-term potential [25]. Details on the technology are not yet disclosed.

As discussed in Section 5, a high flux reactor can have enough production capability by much simple way compared to fission Mo production. The problem is its very low specific activity. Unless a new technology producing high specific activity ^{99}Mo by the (n,γ) method is invented, every effort to increase the specific activity such as irradiation of enriched ^{98}Mo at high neutron flux will be needed. World Nuclear News [26] informed that B. Wortbeek invented a ^{98}Mo(n,γ) method for the production of high specific activity ^{99}Mo. As the Szilard-Chalmers enrichment seems to be utilized for this invention, it was reviewed as described in appended Section A.5. The review concluded that the positive effect of Szilard-Chalmers enrichment is not expected for the mass (n,γ)^{99}Mo production. Though it is too early to judge its feasibility due to no detailed information disclosed, it seems that practical application of this invention is doubtful.

4.4.3 Solution fueled reactors

In January 2009, B&W announced that they made a contract with Covidien for the supply of about half of US demand in ^{99}Mo if they succeed in the development of new reactor and ^{99}Mo separation technologies. This technology extracts ^{99}Mo directly from solution fuel of 100 ~ 200 kW reactor. The status of this technology is well documented in the IAEA-TECDOC-1601 [27] published as a result of IAEA consultancy meeting held in June 2007. An IAEA CRP titled "Feasibility Evaluation of the Use of Low Enriched Uranium Fuelled Homogeneous Aqueous Solution Nuclear Reactors for the Production of Short Lived Fission Product Isotopes" is being implemented and its first Research Coordination Meeting (RCM) was held during 22-26

February 2010 in Vienna, Austria [24].

Demonstration productions by this idea had been twice at the Argus reactor of Kurchatov Institute in Russia, and results of experiments were analyzed at Argon National Laboratory (ANL) in USA and Institute of Radioactive Elements in Belgium as well. ANL [28] developed a concept of 100 kW MIPS (Medical Isotope Production System) during 2000 ~ 2003 through a contract with the Kurchatov Institute and offered industry for funding to technology transfer in October 2009. Milestones of B&W [29] is to operating four 200 kW MIPS in 2014. Meanwhile, China [27] studied the MIPS during 1997 ~ 2007 and a project to construct a 200 kW MIPS is underway.

As mentioned in Section 4.2, about 2 MW fission power is needed to cover current world demand which is assumed about 10,000 six-day-Ci/w. If the 200 kW MIPS is successfully developed, about 20 units are needed to cover the world demand assuming 200% peak production capability to secure the continued stable supply. When the number of units is compared to conventional research reactor type dedicated to ^{99}Mo production such as MAPLE, it is about 10 times. The much low production capability per unit, however, allows region wise distributed production.

For the case of East-Asian region, when the ^{99}Mo is produced by local facilities, supplying about 1,500 six-day-Ci/w was estimated sufficient [30], which requires about 300 kW steady fission power in the targets. Then, four 150 kW units will be needed for the 200% production capability. If it is assumed that the 200 kW MIPS project of China will be successful for the long term stable production of ^{99}Mo, if the 60 MW CARR which reached initial criticality on 13 May 2010 produces fission Mo for the regional supply, and if the HFETR and MJTR continue production of (n,γ)^{99}Mo, then an additional MIPS of 150 or 200 kW would be enough for the region.

However, challenges pointed out in the IAEA-TECDOC-1601 must be resolved. They are categorized by efficient isotopic separation technology, safe level of power density and licensing. As an example showing the degree of uncertainty in the available data for the solution fueled reactors, the safe level of power density is explained here.

As explained above, since the ^{99}Mo production capability of a MIPS is rather small, many units are needed to cover a large demand especially in USA. The most effective way increasing the production capability is increasing the power density, and the current design targets are in the range of 2 ~ 2.5 kW/L. Even though approximately 30 aqueous solution reactors (AHRs) had been built, the safe level of power density is not so clear. From operating experiences of two 50 kW reactors in USA in 1960s, the TECDOC quoted approximately 1.8 kW/L as the safe level of maximum average power density. It is also mentioned that below 2 kW/L may be required to ensure core thermal stability based on experiments from SUPO and KEWB. But tests performed at French SILENE that is designed to operate at about 0.3 kW/L of steady state mode were unsuccessful at higher levels. An old report [31] on the AHRs wrote that JRR-1 was a 62 kW AHR, but a data sheet of JAERI-M 4506 shows that it is 50 kW with 1.9 kW/L core average power density.

The limitation in power density basically comes from the large negative reactivity coefficient of void and temperature in the AHR. It gives the AHR an inherent nuclear safety characteristic against reactivity insertion accident, but causes difficulty in steady state power control at high power density. Operation of MIPS must be very reliable with high availability, which has not been experienced in the actual operation of AHRs.

4.4.4 Photo fission of ^{238}U

Canadian government supported a Task Force on Alternatives for Medical Isotope Production formed in late summer 2008 to discuss, analyze, and evaluate options for using high-power accelerators to generate large quantities of medical isotopes for Canada and its global markets. The Task Force [14] recommended a photo-fission method using ^{238}U targets. In April 2009, MDS-Nordion contracted with TRIUMF (Tri-University Meson Facility) for a feasibility study on this method. As the energy of photon having peak reaction cross section is about 15 MeV, the photon to be used is identical with high energy γ-rays.

For the use of high-power electron accelerators to produce the ^{99}Mo by photon, they compared ^{100}Mo(γ,n) and ^{238}U(γ,f) reactions. It was noted that cross sections of both reactions are about the same, which means that ^{99}Mo yield per photon by ^{238}U(γ,f) is about 6% (fission yield of ^{99}Mo) of ^{100}Mo(γ,n). However, they chose the ^{238}U(γ,f) rather than the ^{100}Mo(γ,n), because the low specific activity of ^{99}Mo by the ^{100}Mo(γ,n) requires major change in the generator technology and enriched ^{100}Mo is quite expensive. However, they did not have enough time to fully consider the economic competitiveness of the accelerator option.

They estimated that ^{99}Mo production per g-U is about 1/200 of conventional fission Mo using HEU. Then too much radwaste will be produced compared to conventional fission Mo method. Therefore, they also mentioned that preliminary novel concepts for electron beam targets could increase it to 1/4 from the 1/200. However, the novel concepts were not disclosed. If they achieve the 1/4, the amount of radwaste containing fission products per unit ^{99}Mo production would be similar with the LEU fission Mo using neutrons. They also guess that the electricity consumption for the operation of accelerators will be very high and that a strong and focused R&D program is required to validate the technology.

TRIUMF was proposing to build a new accelerator as a part of its decadal vision for research. They expect that a low-power test to generate ^{99}Mo with a photo-fission accelerator on a timescale of a few years will be possible at TRIUMF using this device. If the reliable production of ^{99}Mo at reasonable cost is verified through the test, construction of accelerators for actual production of ^{99}Mo by the photo-fission will be commenced. But it is not certain how long it will be actually needed for the test. Furthermore, there are challenging new ideas to be confirmed whether they will actually work.

Therefore, the success of technology is not certain, and if it is successful, rather long time will be needed until this technology can be used for actual ^{99}Mo supply.

5. Mass production feasibility of (n,γ)^{99}Mo

5.1 Neutronics for the (n,γ)^{99}Mo production

Thermal neutron cross section of ^{98}Mo(n,γ) is about 1/5000 of ^{235}U(n,f) as shown in Table 3. As the fission yield of ^{99}Mo from the ^{235}U(n,f) is about 6%, the ratio of ^{99}Mo production cross sections increase to about 1/300. Since it is still very small, it may be supposed that the ^{99}Mo production capability of ^{98}Mo(n,γ) cannot be comparable with the fission method.

However, as found in a study for HANARO [30], the ^{99}Mo production capability of ^{98}Mo(n,γ) can be comparable with that of fission Mo. It is possible by irradiating high density enriched ^{98}Mo targets at high neutron flux. There are basically four factors which make it possible – contribution of epithermal neutron reaction, high neutron flux, high target loading and shorter decay time. Among them, the high target loading can increase the ratio about 30 times and about tenfold can be achieved by other three factors.

Figure 6 shows that the portion of resonance reaction in the ^{235}U targets is small but that in ^{98}Mo targets can be significant under hard neutron spectrum. While irradiation of uranium targets at hard neutron spectrum gives little gain from the epithermal neutron, it produces more ^{239}Pu especially from LEU targets, which gives negative impact to the ^{99}Mo production. For the case of ^{98}Mo(n,γ) reactions, the epithermal neutron reaction rate can be equivalent to or a few times of the thermal neutron reaction rate depending on the target design and neutron spectrum.

The production capability is basically proportional to the neutron flux and target loading allowed in the given irradiation space, but there is limitation for the safety of the irradiation and also by neutron self shielding. The governing factor of the irradiation safety is target temperature. While the majority of heat source for the ^{98}Mo(n,γ) is gamma heating which is within several W/g, the fission energy per unit mass of uranium targets is about 1000 times of Mo targets. Furthermore, decay heat of the fission Mo targets must be safely cooled in the hot cell and/or target transport cask after irradiation as well, as explained in Section 4.2. Therefore, the loading of ^{235}U in the fission Mo targets is very small compared to the available irradiation space, and the loading must be reduced if the neutron flux is very high.

As the neutron capture cross section of Mo is very small compared to the ^{235}U, neutron self shielding is also very small. It allows much heavier loading of ^{98}Mo than the ^{235}U. As shown in Figure 8, ^{98}Mo cross sections are much smaller than the natural Mo. Therefore, if enriched ^{98}Mo targets are used, the neutron self shielding effect becomes smaller than the use of natural Mo targets. However, the resonance self shielding of ^{98}Mo is rather significant at very high ^{98}Mo loading.

The uranium targets require decay heat cooling after irradiation and the post processing is complicated and time consuming. 30 h in total is assumed for the LEU fission Mo production at the MURR [17]. For the case of ^{98}Mo(n,γ), no decay heat cooling is needed and the post process is very simple. Therefore, the decay time can be shortened by more than one day from that of fission Mo.

5.2 Available irradiation targets

MoO_3 is the most popular chemical form of targets for the (n,γ)^{99}Mo production. Its material properties are shown in Table 4. It is chemically stable and its post processing is easy by dissolving in the NaOH solution. Since it is usually available in powder form, the powder is irradiated for small production. The pellet irradiation for the large production requires an additional process converting the powder to pellets. JAEA [1] recently improved density of pellets from 3.4 to 4.45 g/cm^3, which is almost 95% of theoretical density. Data for solubility of MoO_3 in the water are not consistent as shown in Table 4. An internet search shows that it is expressed as insoluble or soluble depending on the purpose of the website. Based on various data searched, it is judged that the solubility may be rather sensitive to temperature, and at least 0.5 g-MoO_3/L is expected, which is significant from the view point of radioactivity release to the coolant. How much and how fast the MoO_3 is washed out from the pellets determines degree of protection such as single barrier or double barriers of irradiation can. The double barriers, of course, reduce the target volume and increases heat resistance. If the ^{99}Mo production capacity is small compared to intended capability to produce, a study on the realistic wash out of Mo from the MoO_3 pellet may be needed.

If the irradiation of the MoO_3 pellets is not sufficient for the ^{99}Mo production, irradiation of a larger density and volume Mo may be considered with additional burdens on processes in target preparation and post processing, including production and collection of relevant data. Potential materials are MoO_2 and Mo metal.

On January 9, 2010, it was written in Wikipedia "*The MoO_2 is insoluble in water, alkalis, HCl and HF, slightly soluble in hot H_2SO_4, and has a theoretical density 6.47 g/cm^3. It is a violet-colored solid and is a metallic conductor*". Its water insolubility and higher density than MoO_3 may open a possibility for a larger production of ^{99}Mo, but technical feasibility for the target preparation and post processing must be duly investigated.

The Mo metal allows the highest target loading. Its material properties are listed in Table 5. The Mo metal has the sixth-highest melting point of any element and burns only at temperatures above 600 °C. It has one of the lowest thermal expansion coefficients among commercially used metals. Its thermal conductivity is excellent. It does not react with oxygen or water at room temperature. At elevated temperatures, MoO_3 is formed.

S. Okane et al [32] tested natural metal Mo as a target for the ^{99}Mo production. They reported significant neutron self shielding effect and a Mo metal dissolution by a nitro-hydrochloric acid. Dissolution of Mo metal is much more difficult than the MoO_3, especially for bulky substance. A mixed target of tiny Mo metal shots and water reduces the neutron self shielding as well as the difficulty in dissolution. In this case, about 6 g-Mo/cm^3 loading can be achieved rather than the 10.2 g/cm^3.

An actual target material can be selected based on estimations for the specific activity and production capability. While a higher Mo loading gives a higher production capability, the specific activity becomes lower due to the higher neutron self shielding, which is especially significant for natural Mo targets. If the production capability is enough, however, an irradiation volume for the high Mo density targets can be reduced to the high flux area and a higher specific activity can be obtained.

Use of enriched ^{98}Mo targets not only enhances ^{99}Mo production capacity but also increases specific activity. Neutron self shielding effect becomes less as well due to the lower absorption cross sections of ^{98}Mo than the natural Mo. But it is expensive. The price of enriched ^{98}Mo may depend on quantity, enrichment and chemical form for every specific order. In 1998, KAERI purchased 98.5% enriched $^{98}MoO_3$ from a Russian company to expand ^{99m}Tc supply to cope with sudden price increase of imported ^{99m}Tc generators due to sudden degradation of Korean currency. Recent quotation from the same company in February 2009 was about 1.5 times of the previous price, which seems reasonable if the escalation during 10 years is taken into account. It was supposed that the price portion of enriched ^{98}Mo in the production of ^{99}Mo at HANARO was reasonable compared to the price of imported ^{99}Mo solution in 2008. Since recovering Mo from spent generators is a simple process, recycling of enriched ^{98}Mo may also be considered.

5.3 Considerations in the design of an irradiation facility for mass $(n,\gamma)^{99}$Mo production

As discussed in Section 5.1, the mass production of $(n,\gamma)^{99}$Mo can be achieved at the high thermal and epithermal neutron flux hole which is located inside or near the core under fast flow of coolant. While the reactor operation is not a weekly mode, a hydraulic rabbit system (HRS) is needed for the on-power loading and unloading of targets at such irradiation hole. Installation of a HRS inside the core is not easy because of neutronic impact to the core not only from the installation of the HRS but also from the on-power loading and unloading of targets, as well as interference of the HRS with handling of core materials including fuel. Therefore, an irradiation hole near the core boundary is usually a proper place.

For the convenience' sake to explain, a conceptual cut view of the HRS irradiation part installed in the irradiation hole with targets is drawn in Figure 7. The HRS irradiation part consists of two coaxial pipes (HRS inner and outer pipes in the figure) loaded at a hole in the Be or Heavy water region. For the case of Be reflected reactor, the irradiation hole can be made in the Be or Al block. For the case of heavy water reflected reactor, unless it is cooled by the heavy water as well, an Al or Zr pipe installed in the heavy water tank makes the irradiation hole. The rabbits containing the targets are loaded at the center of the HRS inner pipe.

If the target is soluble in the coolant, the rabbit should have double containments against leakage of target material to the coolant in case rabbit outer wall fails. The water gap between rabbit outer wall and HRS inner pipe (Water Gap-1 in the figure) should be sufficient to cool the rabbits. The water gap between inner and outer pipes of HRS (Water Gap-2) is a part of flow path for the transportation and cooling of the rabbits.

The production capability can be increased by maximizing neutron flux at the targets and target loading in the high flux zone. If possible, first of all, the maximization of neutron flux is desired, because it increases the specific activity as well. The increase of target loading can be accomplished by increasing target density and volume.

The target volume can be increased by increasing target diameter and total length of targets. If possible, however, increasing the target diameter is more effective because axially high flux region can be utilized. Increasing the target radius increases the neutron self shielding too, but it would be sufficiently compensated by the higher neutron flux achieved by reducing the target length.

Maximizing the neutron flux is basically achieved by selecting good neutron economy materials for the HRS and its surrounding material in the neutron flux region. If the inner and outer pipes can be made of Zr or Al, a combination with the good reflector material will give the highest neutron flux at the targets. For the case of a pressurized closed vessel type research reactor as JMTR, however, it may not be easy. The outer pipe of HRS located inside of the reactor vessel becomes pressure boundary of the primary coolant and its integrity is very important for the reactor safety. Therefore, a stainless steel (SS) pipe with sufficient thickness as the pressure boundary would be the only practical choice. If the irradiation performance of Zr pipe is fully verified, it may be used only the part under considerable neutron flux, and the connection between the Zr and SS pipes can be accomplished by the friction welding. While the outer pipe is SS, the Be block enclosing the HRS pipes does not have a special advantage for the increase of neutron flux at the target, because a large portion of neutrons slowed down in the Be is lost in the SS pipe.

Unless the neutron spectrum is very hard, thicknesses of water gaps should be minimized. When the HRS outer pipe is SS, it is especially important because the neutrons slowed down by the water will be lost by the SS. Since the heat generation in the target is low, the flow rate required at the Water Gap-1 is not so high. Reduction of the water gaps, however, increases pressure drop especially in Water Gap-2, which is not desired. While the length of Water Gap-1 is determined by the total length of rabbits, Water Gap-2 extends to the whole length of coaxial pipes. If the inner diameter of HRS outer pipe can be enlarged at some place above the irradiation hole, the pressure drop can be significantly reduced.

If the target is Mo metal, a metal target shaped as the rabbit without any cladding can be used. The release of ^{99}Mo and ^{99m}Tc to the coolant will be much less than the release of Al activation products to the coolant when it is clad by Al. Since the Al can is the major radwaste in the (n,γ)^{99}Mo production process, there will be almost no radwaste. If the target is Mo metal shots, the shots can be contained in the perforated Al can allowing mixing of water with the Mo metal shots.

When MoO_3 pellets are used for the targets, it is not certain whether how much Mo will be dissolved in the water from the MoO_3 pellets when the clad fails. If the MoO_3 pellet is easily dissolved in the water, the double containment is certainly needed. However, if the dissolution rate is sufficiently slow and the leakage can be detected sufficiently early for a remedial action to be taken without any significant radiological consequence, then a single containment rabbit may be used. Of course, an experiment on the dissolution rate of the MoO_3 pellet in the flowing water is necessary. A conceptual analysis on a possibility of online monitoring against the leakage is as follows:

Major activation products to be released to the rabbit coolant during normal operation are produced by $^{16}O(n,p)^{16}N$, $^{27}Al(n,\alpha)^{24}Na$, $^{27}Al(n,p)^{27}Mg$, $^{27}Al(n,\gamma)^{28}Al$ and $^{40}Ar(n,\gamma)^{41}Ar$ reactions. The ^{16}N is produced by an activation of oxygen in the water. Since its half-life is only 7.13 s, it is sufficiently decayed out in a decay tank of the HRS. Majority of other activation products except the ^{41}Ar are cleaned up at the ion exchanger. While majority of metallic ions are positive ions, activation products of MoO_3 dissolved in the water are in a chemical form of $^{99}MoO_4^{-2}$ and the daughter ^{99m}Tc. Therefore, if the ion exchanger is composed of a cation exchanger column and an anion exchanger column in series, the $^{99}MoO_4^{-2}$ only will accumulate at the anion exchanger column, and an abnormal release of the MoO_3 would be easily detected by an online gamma monitor looking at the anion exchanger column. If the single containment rabbits can be used by above measure, the diameter of target is increased, the temperature rise at the gas gap between inner and outer wall of rabbit (Gas Gap-1) is eliminated, and Al waste is reduced.

However, the low heat conductivity of MoO_3 requires confirmation on its temperature, especially when the target diameter is maximized for the maximum production of ^{99}Mo. The melting point of MoO_3 is 780 °C and its sublimation temperature is around 750 °C [33]. Therefore, a maximum temperature of the MoO_3 during irradiation may be limited below the sublimation temperature. JAEA measured heat conductance of 3.28 g/cm^3 MoO_3 pellet and made following correlation which can be used for 60 °C ~ 300 °C range [33].

$$k_p = 2.07 - 2.05\times10^{-3}T - 4.64\times10^{-6}T^2 + 1.38\times10^{-8}T^3 \qquad (1)$$

where, K_p is heat conductivity in W/m-K and T is pellet temperature in °C. Above equation is depicted in Figure 8. The average conductivity in the 60 °C ~ 300 °C range is 1.65 W/m-K.

JAEA also succeeded manufacturing of 4.45 g/cm^3 MoO_3 pellets [34]. Therefore, it is assumed that the 4.45 g/cm^3 MoO_3 pellets are used for the targets. The thermal conductivity increases as the pellet density increases, but the average for 3.28 g/cm^3 pellet is used for the estimation of pellet temperature, taking into account the decreasing trend of conductivity with temperature as shown in Figure 8.

A temperature rise from the surface of MoO_3 pellet to its center line is the most limiting factor from the viewpoint of target cooling. The temperature rise (ΔT) can be roughly estimated by following equation.

$$\Delta T = \frac{q'}{4\pi \overline{k_p}} = \frac{R^2 q'''}{4\overline{k_p}} \tag{2}$$

where, $\overline{k_p}$ is the average heat conductivity of pellet, R is radius of pellet, q' is linear heat rate and q''' is volumetric heat rate.

Assuming 6 W/g gamma heat in the 2 cm diameter pellet of 4.45 g/cm^3 density, the calculated ΔT is 405 °C. Should the bulk temperature of rabbit coolant and additional temperature rises at two gas gaps inside the rabbit and at the rabbit surface be added, a margin to the sublimation temperature 750 °C may not be large enough. As the ΔT is proportional to the square of pellet diameter, the margin to increase the pellet diameter is very limited.

In order to minimize the pellet center temperature, two gas gaps inside the rabbit must be minimized so as to reduce a thermal resistance at the gaps as well. For a meaningful increase of the pellet diameter, however, a new annular target of which concept is shown in Figure 9 is suggested. As the water flows through holes at the center of targets as well, the maximum pellet temperature is easily reduced. It has an additional advantage from the neutronics point of view. Without the water hole, the ^{99}Mo production rate at the central part is the lowest in the pellet due to the neutron self shielding especially the resonance self shielding. As the water in the hole scatters down fast and epithermal neutrons, at the central part of the pellet, the resonance self shielding is reduced and a certain increase of thermal neutron flux is expected. The pellet volume is reduced by the hole, but its portion in the pellet is small. A practical disadvantage would be a higher cost for the manufacturing of rabbits.

The effect of cooling by the central hole can be estimated from a heat balance equation for the cylindrical geometry.

$$\frac{d(krT')}{dr} = -rq''' \tag{3}$$

where, r is radius in the pellet. If it is assumed that the q''' and the thermal conductivity k is constant, a solution for above equation becomes Eq. (4).

$$T(r) = a\ln(r) + b - \frac{q''' r^2}{4k} \tag{4}$$

where, a and b are constants to be determined from boundary conditions. When there is no hole at the center, $a = 0$ and the temperature rise in the pellet becomes Eq. (5).

$$\Delta T(r) = T(r) - T_s = \frac{q'''}{4k}(R^2 - r^2) \tag{5}$$

Figure 10 compares theoretical temperature rises inside 4 cm diameter pellet for the same gamma heat and conductivity as previous case. Without the cooling hole at the center, its center line temperature is about 1,600 °C higher than the surface. When the pellet has a 0.6 cm radius hole and its inner surface temperature is the same with the outer surface, the temperature rise is about 400 °C, which is similar the case for the 2 cm diameter pellet without hole. In this case, the heat flux at the inner surface is about 1.5 times of outer surface. Therefore, the inner surface temperature will be higher than the outer surface. The figure also shows cases when the inner surface temperature is 50 and 100 °C higher than the outer surface. The effect of inner surface temperature to the highest temperature in the pellet is about a half of its variation.

Above analysis indicates that the temperature of large diameter pellet can be maintained below safe level by additional cooling hole at the center of the pellet. While it is intended to use the new high density MoO_3 pellet, a measurement of its conductivity is basically needed in any case, so as to predict realistic pellet temperature and to confirm the irradiation safety.

When the irradiation hole is just outside of the core, the nuclear perturbation from the on-power loading and unloading of rabbits may not be sufficiently small to neglect, especially when the enriched ^{98}Mo is used in the maximized diameter rabbit. While there is no rabbit in the irradiation hole, the water occupies the hole. When the rabbits are loaded into the irradiation hole, some of the water is replaced by the rabbits and the neutron loss is reduced. Therefore, the loading of rabbits will increase the reactivity. It will change neutron flux and power distribution nearby as well. Such nuclear impacts shall be checked for the design of a HRS.

If the impacts from the on-power loading and unloading of rabbits are rather large and if a way to reduce the impacts is necessary, following idea may be considered: If an object having similar neutronic characteristics with the rabbits occupies the irradiation position whenever the rabbits are withdrawn, the nuclear impact can be reduced. An empty aluminum can which floats in the water would be a good candidate simulating the rabbits. The rabbit is composed of aluminum can(s) and MoO_3 pellets, of which neutron slowing down power is much smaller than the water. From the view of neutrons, the rabbit is rather transparent and closer to a void rather than the water, especially when the enriched ^{98}Mo is used. The thick water is opaque to neutrons as usually visualized by neutron radiography. The void does not absorb neutrons but a neutron leakage will increase. Total length of the void aluminum can may be adjusted for a further optimization.

Figure 11 shows a concept utilizing the void aluminum can as a floater. Above the rabbits, the inner pipe has a valve operated by the floater. When rabbits are being unloaded, the flow direction in the inner pipe is reversed from down flow as (c) in the figure to up flow, rabbits come out of the pipe, the floater moves upward, and then the valve is open as (a) in the figure. In this case, as the floater replaces the irradiation position of rabbits without any time gap, little nuclear impact is expected. When the flow direction is reversed again to load new rabbits, it will become (b). In order to prevent the floater from moving down before rabbits arrive at the top of floater, the down flow would be increased gradually. The status of (b) is uncertain whether the floater will move down earlier than the arrival of rabbit. If the floater is at the (b) hopefully until the rabbits arrive, then the floater moves downward with the rabbits, and finally the status (c) will be reached. The bottom of the inner pipe can be made as a hydraulic damper to absorb a mechanical impact from rabbits when they hit the floater.

This concept can be applied when the inner pipe has a sufficient space to install the floater underneath the rabbit irradiation position and the floater has a sufficient buoyancy force. The diameter of floater must be larger than 10 times of aluminum thickness so as to be floated by the buoyancy force of water.

Figure 12 is a conceptual view of the floater while rabbits are under irradiation. When the flow inside the inner pipe is downward, a hole at the bottom of the inner pipe is closed by a ball. When the flow direction is reversed to unload rabbits, the ball floats, the hole at the bottom is open, the floater moves upward with the rabbits, and it becomes Figure 11 (a). When the floater is not moving at the Figure 11 (a), the ball closes the hole at the bottom. When the flow is reversed again to load rabbits, the floater is at (b) by its buoyancy force, the floater moves downward when rabbits hit the floater, and the lowest part of the inner pipe functions as a hydraulic damper absorbing the impact from the rabbits.

6. Concluding remarks

Due to the short half-life of ^{99}Mo, its continued supply is very important for the on-time availability of ^{99m}Tc at hospitals. As the capability of fission method for mass production of high specific activity ^{99}Mo allows few reactors to cover majority of world market, however, the world depends on the few primary reactors producing fission Mo, which consequently has a risk to the continued supply. The current severe shortage of ^{99}Mo proves the risk and recalls the importance of self sufficient regional supply.

Since USA consumes about a half of the world ^{99}Mo without any domestic production, the impact from the shortage must be much severer than other countries. They are now implementing the American Medical Isotopes Production Act for the ^{99}Mo production in USA without HEU. They made contracts with two companies to develop ^{99}Mo production technologies using solution fueled reactors and (n,γ) method, and are contacting with industry for the use of LEU targets in the reactors and for the use of accelerator technology.

Research reactor operators in Europe announced their position concerning the current shortage of ^{99}Mo. They emphasized that production of ^{99}Mo at all available research reactors in Europe is the most practical way from near to long term stable availability of ^{99}Mo in Europe.

If USA succeeds the self sufficient production of ^{99}Mo from 2013 as above Act aims, they can push the conversion of fission Mo targets at foreign reactors from HEU to LEU much strongly. Since the weight of radwaste from the LEU targets is about five times of that from HEU, the production of LEU fission Mo may raise an ethical issue for the fission Mo supply to other regions, in addition to the cost issue for the conversion to LEU. The new productions in USA and Europe will take into account the full cost not only for the normal production for the supply to respective regions but also for the installation and maintaining of backup capability for other regions, into the price of ^{99}Mo. Therefore, much higher price of ^{99}Mo in the future than before is foreseen.

East-Asia is the third largest market of ^{99}Mo in the world, but heavily depends on import from other regions. Only China produces ^{99}Mo but may not be enough for the stable availability even in China alone. Other countries entirely depend on import from North America, Europe and South Africa. However, regional actions to establish a concrete scheme for the long term stable availability of the ^{99}Mo in the region are rather weak compared to USA and Europe.

As discussed in appended Section A.3.3, the frequency of medical inspections using the ^{99m}Tc per unit population in the region is much less than USA or Europe. Since the unit frequency is very dependent on the living standard, China will show increasing demand for a while. In Japan, the annual total frequency is at the post saturation status with gradually decreasing trend. As the average life span of Japan has been increasing, actual number of patients who need inspections using ^{99m}Tc may be increasing. Therefore, the decreasing trend would be due to the replacement by PET. Korea has shown almost steadily increasing trend during past two decades and the recent unit frequency is very close to Japan. Taiwan would be similar with Korea. Therefore, the current unit frequency of Japan would be a good indicator for the prediction of maximum unit frequency of the region in the future. It is some less than 1 %/person-year, which is less than 20% of USA. The unit frequency in Europe is in between USA and Japan. We do not understand why the unit frequency of the region is much lower than USA and Europe. We simply suppose that an actual peak value of the unit frequency of the region will be sufficiently less than 1 %/person-year due to the rapid increase in the use of PET.

Based on above unit frequency and population, the future ^{99}Mo demands for China, Japan and Korea can be estimated about 2,500, 250 and 100 Ci/w, respectively. The ^{99}Mo activities are calibrated values at middle of the week while ^{99m}Tc generators are under use, which are similar values expressed by the six-day-Ci from short distant ^{99}Mo solution suppliers. For the estimation, it was assumed that if the ^{99}Mo is supplied multiple times in a week from short distance, the average usage of ^{99}Mo for an inspection will become similar values regardless of countries. The current demand of China is less than Japan. Therefore, the actual current ^{99}Mo demand of the region is less than 600 Ci/w when the ^{99}Mo is supplied from the region in a reliable manner, which is less than a half of the previous estimation 1,500 Ci/w [30].

Actual ^{99}Mo imports of Japan and Korea were about five and two times of respective national ^{99}Mo demands above mentioned. Japan and Korea basically needed to buy about twice of ^{99}Mo solution to compensate its decay during delivery from long distance. In 2009, however, while the ^{99}Mo import of Korea dropped to about 60% of previous year, the total number of annual SPECT inspections continued the increasing trend. It indicates that international delivery of ^{99}Mo solution and the efficiency using the ^{99}Mo were improved to reduce its decay without usage against its shortage in supply. It would be similar case to Japan. Since Japan has the large room to improve the internal efficiency in the usage of ^{99}Mo, the impact to hospitals in Japan from the current severe shortage of ^{99}Mo supply would not be as significant as USA. For the case of Korea, the internal room to increase the efficiency is smaller than Japan but HANARO can supply ^{99m}Tc solution in case of actual shortage.

Therefore, it seems that actual availability of ^{99m}Tc at hospitals in Japan and Korea are not so significantly impacted compared to the reduction of global ^{99}Mo supply, which may explain one of reasons why the regional actions for the long term stable availability of the ^{99}Mo in the region are weak compared to USA and Europe. Instead, patients have paid higher price than USA and Europe for the ^{99}Mo – more than five times in Japan and about twice in Korea, but it has been hidden in their total payment. However, the fact that production of fission Mo in Japan and Korea is actually very difficult should also be pointed out as a reason causing the weak regional actions for the long term availability of ^{99}Mo.

Establishing a reliable fission Mo supply scheme of the region is very difficult. Actually it is very difficult at every region. Otherwise the shortage of ^{99}Mo cannot be the global issue anymore. A typical example is the long story of USA to establish a self supply scheme but not successful so far. The key point is that new facilities are very expensive compared to the market price of ^{99}Mo. Furthermore, redundancy of such expensive facilities is basically required to guarantee the reliable availability of the fission Mo. As the region-wise supply scheme requires more facilities than the global supply scheme, it is more expensive. However, as aforementioned, USA and Europe intend to establish the expensive region-wise supply scheme based on the lesson learned from the shortage,

Establishing the fission Mo supply scheme of this region is much more expensive than USA and Europe. First of all, the market is much smaller. When the ^{99}Mo is produced at local facilities, the market size of Japan and Korea is about 350 six-day-Ci as aforementioned, which is about 6% of USA or 3% of global market. However, more facilities are required to produce the smaller amount of ^{99}Mo than the other regions because of the over sea transportation between any two countries in the region. For example, a chemical facility in China cannot process uranium targets irradiated at reactors of other countries. Therefore, at least two chemical facilities are needed in two countries. If China begins production of fission Mo at CARR and at the solution fueled reactor of which project is under progress, and if their production and the production of Indonesia are available for the backup to Japan and Korea, one more production either in Japan or Korea may be enough. Since availability of an existing reactor in Japan and Korea is about 200 days per year, two reactors irradiating uranium targets and a chemical facility are needed for the production. If the chemical facility is located in Japan, two reactors (JMTR and JRR3) may be available. If a new research reactor capable for the fission Mo production is built in Korea, two reactors may also be available for the chemical facility located in Korea. If the construction of a new research reactor in Korea is decided, the production in Korea would be better because the new reactor can be designed by considering the fission Mo production in combination with the chemical facility. Then there are five reactors and three chemical facilities to secure the fission Mo supply to this region. If it is compared with the fact that more than 95% of global ^{99}Mo market is covered by five reactors and four chemical facilities, we can easily figure out that the fission Mo production in this region for the self sufficiency is extremely expensive.

JAEA has been studying the (n,γ)^{99}Mo production at JMTR, which encouraged a feasibility study for HANARO in KAERI. The previous study confirmed that an irradiation hole of HANARO located near the boundary of core has enough capability to satisfy the regional demand by irradiating high density enriched $^{98}MoO_3$ pellets. There are five research reactors in the region for the potential (n,γ)^{99}Mo production - two each in China and Japan, and one in Korea. If they are operated in a concerted mode for the production of (n,γ)^{99}Mo, it can be an effective way for the stable availability of ^{99}Mo in the region. This study confirms that it will be technically feasible.

For the irradiation of targets, each reactor should have an appropriate target irradiation system, which is much easier and less expensive than the fission Mo target irradiation facility for its installation and operation. The neutron flux at the irradiation hole should be high enough and enriched ^{98}Mo should be used in case a certain minimum specific activity which cannot be satisfied by the natural Mo target exists. The enriched ^{98}Mo is quite expensive, but its price for an irradiation target is sufficiently small compared to the price of equivalent ^{99}Mo solution to be produced. The target irradiation should be flexible - multiple targets from different customers loaded at different timing can be irradiated. The quick and easy loading and unloading of targets in the hydraulic rabbit system enables the flexible irradiation.

Irradiated targets are immediately transported to the ^{99m}Tc generator manufacturers and major radiopharmacies in the bare solid form ready for dissolution for their products. The ^{99}Mo solution suppliers who operate complicated and expensive hot cell facilities for chemical process of fission Mo targets and have shared majority of cost in the current production, no more exist in the supply chain of (n,γ)^{99}Mo. Since the reactors are involved only for the target irradiation, almost no concern in the medical license for different reactors is expected.

The ^{99m}Tc generator manufacturers may use PZC and ALSUL for the generator columns. The PZC has some limitation for the mass production of generators, but is almost ready for the commercial use for medium scale production. The ALSUL was tested for the $^{188}W/^{188}Re$ generator and is currently under test for the $^{99}Mo/^{99m}Tc$ generator. Since its generator loading process is the same as conventional alumina column loading using fission Mo, it is expected that mass production of ^{99m}Tc generators will be possible. The use of PZC or ALSUL generator in the hospital is expected almost equivalent with the use of conventional fission Mo generator. They may need works during holidays to maximize the activity of generators that they offer and cost for the manufacturing process of generators will be higher than those for conventional process using fission Mo, but it may be sufficiently compensated by the low cost for the $(n,\gamma)^{99}Mo$ production.

The major radiopharmacies are currently operating the Master milkers. They may utilize well proven solvent extraction technology to extract high concentration ^{99m}Tc or may make large PZC or ALSUL columns connected to ^{99m}Tc concentration devices. Therefore, the work load to the radiopharmacies will become heavier than the use of Master milkers, but it may be sufficiently compensated by the low cost for the $(n,\gamma)^{99}Mo$ production as well.

Since the major concern of medical license is limited to the generator manufacturers and radiopharmacies in each country, the licensing process is simple. The uncertainty in the above procedure is whether the ALSUL and the use of solvent extraction method to large scale process will be successfully verified. Test of the ALSUL is under progress. The solvent extraction technology is well proven for the process up to a few decades of Ci. As there has been no experience using it at the activity level of Master milker (500 Ci), the verification is needed. But no serious problem is expected from the technical view point. It is clear that these verifications are much easier than any other approaches to find out new sources of ^{99}Mo.

The study also proposes heat conductivity measurements for the high density MoO_3 pellets and tests on its dissolution characteristics in the flowing water for the effective design of $(n,\gamma)^{99}Mo$ targets.

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REFERENCES

[1] Medical Isotope Production Without Highly Enriched Uranium, Nuclear and Radiation Studies Board, Division of Earth and Life Studies, NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, THE NATIONAL ACADEMIES PRESS, Washington D.C. www.nap.edu, 2009.

[2] Myers WG. Georg Charles de Hevesy: the father of nuclear medicine *J Nucl Med* 1979; 20, pp.590-594.

[3] P. Richards, A survey of the production at Brookhaven National Lab of the isotopes for medical research, *Trans.* 5th *Nucl. Cong.*, 7th *Int. Electr. Nucl. Symp.*, Rome (1960).

[4] Technetium-99m Radiopharmaceuticals: Manufacture of Kits, Technical Reports Series No. 466, IAEA, Vienna, 2008.

[5] Kocher, David C., Radioactive decay data tables, DOE/TIC-11026 (1981).

[6] C. Morillon, et al, Table de radionucléides, BNM-LNHB/CEA, http://www.nuclide.org/ DDEP_WG/Nuclides/, read on 3 March 2010.

[7] Labelling of small biomolecules using novel technetium-99m cores, Technical Reports Series No. 459, IAEA, Vienna, 2007

[8] Bruce J. Barron, et al, Mysterious Radiopharmaceutical Localization: A Pictorial Interactive Exhibit, The University of Texas-Houston Medical School Houston, Texas, www.uth.tmc.edu/radiology/exhibits/2007/ARRS_barron_2006.pps, visited on Nov. 27, 2009.

[9] NRC INFORMATION NOTICE 2008-22: MOLYBDENUM-99 BREAKTHROUGH IN MOLYBDENUM-99/TECHNETIUM-99M GENERATORS ADDRESSEES, January 12, 2009.

[10] AM Millar, Effect of source and age of sodium pertechnetate Tc 99m on radiochemical purity of technetium Tc 99m exametazime, American Journal of Hospital Pharmacy, Vol 50, Issue 1, pp.103-106, 1993.

[11] Technetium Tc-99m Exametazime Kit, Amersham Ceretec kit http://www.orgyn.com/ resources/genrx/D003168.asp, read on 6 April 2010.

[12] R. E. Boyd, The gel generator: a viable alternative source of ^{99m}Tc for nuclear medicine, *Appl. Radiat. Isot.* Vol. 48, No. 8. pp. 1027-1033, 1997, Elsevier Science Ltd., Printed in Great Britain

[13] P. Saraswathy, et al., Tc-99m generators for clinical use based on zirconium molybdate gel and (n,γ) produced Mo- 99: Indian experience in the development and deployment of indigenous technology and processing facilities, 2007 International RERTR Meeting, www.rertr.anl.gov, read on 13 April 2010.

[14] Making Medical Isotopes, Report of the Task Force on Alternatives for Medical-Isotope Production, TRIUMF, Univ. British Columbia, Advanced Applied Physics Solutions, Inc.

with support from Natural Resources Canada.

[15] Yasuki Nagai and Yuichi Hatsukawa, Production of ^{99}Mo for nuclear medicine by ^{100}Mo(n, 2n)^{99}Mo, *J. Physical Soc. Japan*, Vol. 78, No. 3, March 2009.

[16] Bennett, Ralph G., et al, Method for the production of ^{99m}Tc compositions from ^{99}Mo-containing materials, US Patent 5802439, Filing Date 02/19/1997.

[17] Ralph A. Butler and Alan R. Ketring, National Academy of Sciences: National Medical Isotope Production Study, Missouri Research Reactor Center, University of Missouri, http://dels.nas.edu/nrsb/presentations/ralphbutler.pdf. visited 4 December 2009.

[18] S.S. Abalin, et al., Method of strontium-89 radioisotope production, US Patent 6456680, Sept. 24, 2002.

[19] P. Saraswathy, et al., Tc-99m generators for clinical use based on zirconium molybdate gel and (n,γ) produced Mo- 99: Indian experience in the development and deployment of indigenous technology and processing facilities, 2007 International RERTR Meeting, www.rertr.anl.gov, read on 13 April 2010.

[20] J.S. Lee, et al., Development of a high performance ^{188}W/^{188}Re generator by using a synthetic alumina, Applied Radiation and Isotopes, 67 (2009) pp.1162-1166.

[21] G. Krysztoszek, et al., Operation of the Maria research reactor, Operation and Safety of Maria Reactor, Annual Report 2006, Institute of Atomic Energy, http://www.iea.cyf.gov.pl. read on 19 May 2010.

[22] H. Gerstenberg, et al., U-target irradiation at FRM II aiming the production of Mo-99 – A feasibility study, RRFM10, Marrakech, Morocco, 21-25 March 2010.

[23] http://www.healthimaging.com/_news/person/Robert+Atcher. read on 24 May 2010.

[24] IAEA Coordinated Research Project (CRP) on Feasibility Evaluation of the Use of Low Enriched Uranium Fuelled Homogeneous Aqueous Solution Nuclear Reactors for the Production of Short Lived Fission Product Isotopes, Report from IAEA RCM 22-26 February 2010, Vienna, Austria, http://www.iaea.org/OurWork/ST/NE/NEFW/rrg_crp_1548.html, read on 21 May 2010.

[25] http://www.healthimaging.com/, read on 24 May 2010.

[26] http://www.world-nuclear-news.org/, New technique promises non-U medical isotopes, 16 September 2008.

[27] Homogeneous aqueous solution nuclear reactors for the production of Mo-99 and other short lived radioisotopes, IAEA-TECDOC-1601, Sept. 2008.

[28] Technology development for Sr-89 production with 100kW medical isotope production system (“MIPS-100”), ANL/NE-C0000401, 2 October 2009.

[29] E. Reynolds, Medical isotope production system, Covidien Users Group, June 2009, http://www.covidien.com.

[30] B.J. Jun, et al, Revaluation of ^{99}Mo production by (n,γ) method at HANARO, JAEA- Review 2010-032, July 2010.

[31] Wilson, et al, Aqueous homogeneous type research reactors. Second United Nations International Conference on the Peaceful Uses of Atomic Energy, June 1958. http://www.osti.gov/bridge/servlets/purl/4315502-KiRPtd/4315502.pdf.

[32] Shogo Okane, et al, Private Communication, 1985.

[33] Koichi Iimura, et al, Conceptual study of ^{99}Mo production facility in JMTR, JAEA-Technology 2008-035, June 2008 (in Japanese).

[34] Yoshitomo Inaba, et al, Status of development on ^{99}Mo production technology in JMTR, ANIMMA *Intl. Conf.*, 7-10 June 2009, Marseille, France.

Table 1 Radioactive decay data relevant to ^{99m}Tc

	DOE/TIC-11026 [4]	LNE-LNHB/CEA [5]
Branching ratio from ^{99}Mo (%)	88.6	87.6
Half-life of ^{99}Mo (h)	66.02	65.95
Half-life of ^{99m}Tc (h)	6.02	6.0067
Mean energy of major γ-ray (keV)	140.5	140.511
Mean probability per disintegration (%)	89.07	88.5
Majority of other decay	Internal Conversion	Internal Conversion
Half-life of Tc (y)	2.13E5	2.14E5
Mode of decay	β^-	β^-
Maximum (average energy) of β (keV)	293.6 (84.6)	436.3 (152.3)

Table 2 Summary of USP specifications for sodium pertechnetate ^{99m}Tc injection

		Fission Mo	(n,γ)^{99}Mo	Remark
Sterility		Sterile solution		
Bacterial endotoxins		≤175/V USP Endotoxin Unit per mL		At expiration date or time
pH		4.5 ~ 7.5		
Radiochemical purity		≥ 95%		At time of administration
Radionuclide purity (μCi/mCi)	^{99}Mo	≤0.15	≤0.15	
	^{131}I	≤0.05	-	
	^{103}Ru	≤0.05	-	
	^{89}Sr	≤0.0006	-	
	^{90}Sr	≤0.00006	-	
	Others	β & γ emitters ≤0.1 α emitters ≤1x10^{-6}	γ emitters ≤0.5 ≤2.5μCi/dose	
Chemical purity	Al	≤10 μg/mL	≤10 μg/mL	
	Methyl ethyl ketone	-	≤0.1%	

Table 3 Nuclear reactions producing ^{99}Mo

Reaction	Cross section (Energy)	Remark
^{235}U(n,f)	577 (thermal)	Majority of current production, 6.17 %
^{238}U(γ,f)		TRIUMF, similar fission yield as ^{235}U(n,f)
^{98}Mo(n,γ)	0.13 (thermal)	Bert Wolterbeek, JAEA, KAERI
^{100}Mo(n,2n)	1.91 (14.8 MeV)	Yasuki Nagai and Yuichi Hatsukawa
^{99}Tc(n,p)	0.0151 (14.7 MeV)	
^{100}Mo(p,pn)	0.079 [280 MeV]	
^{100}Mo(p,d)		
^{100}Mo(γ,n)		Ralph G. Bennett, et al
^{100}Mo(γ,p)		^{99}Nb ($t_{1/2}$ 15 s), ^{99m}Nb ($t_{1/2}$ 2.6 m) → ^{99}Mo
^{102}Ru(n,α)	0.0034 (14.1 MeV)	
^{98}Mo(d,p)	0.0253 (9 MeV)	

* Source of cross sections: Y. Murakami, et al, Radiation Data Book, Chijinshokan Co. Ltd.(1982).

Table 4 Material properties of MoO_3

Molecular weight	Density (g/cm^3)	Melting point (°C)	Boiling point (°C)
143.94	4.69	795	1155
Appearance Green powder, gray-black powder White, or slightly yellow to slightly bluish, depending on the temperatures Colorless to white or yellow odorless solid			
Solubility in water (g/L) 1.066 (18 °C), 2.055 (70 °C) [Wikipedia (2009.12.21)] 0.5 (20 °C) [www.maxchem.org (2009.12.21)] <1 at 75° F (NTP, 1992) [CAMEO Chemicals, http://cameochemicals.noaa.gov/chemical/8862 (2009.12.21)] 0.49 (28 °C) [Japan Chemistry Society, The Eighth Series of Experimental Chemistry - Synthesis of Inorganic Chemistry I- Maruzen, (1976), p.280.] * MoO_3 nanopowder has a relatively high solubility in water and should not be exposed to liquid water without the presence of protective coatings. [http://www.answers.com/topic/molybdenum-sesquioxide, (2009.12.21)] * Slight solubility in acids			

Table 5 Material properties of Mo metal

Appearance	Molecular weight	Density (g/cm³)	Melting point (°C)	Boiling point (°C)
Silvery grey metal	95.94	10.2	2,610	4,825

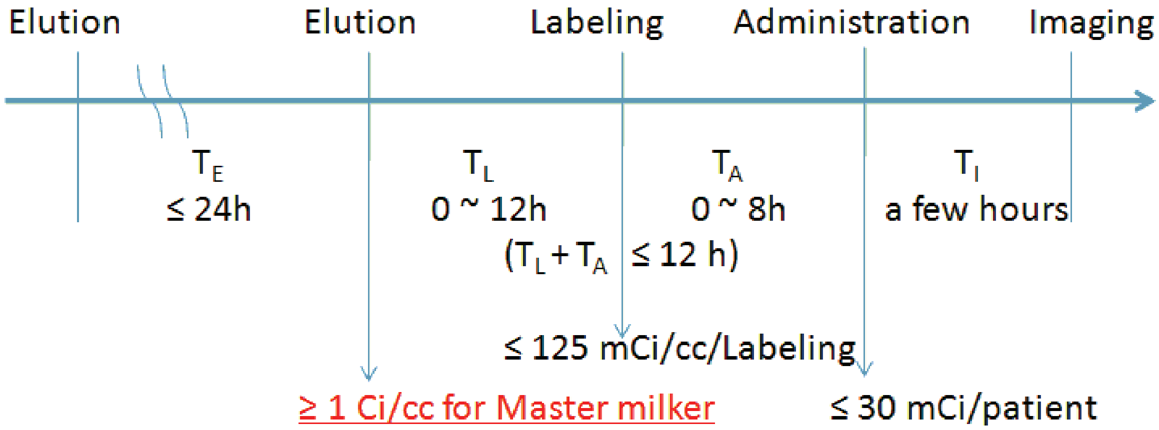


Figure 1. Time intervals and activities for the use of ^{99m}Tc

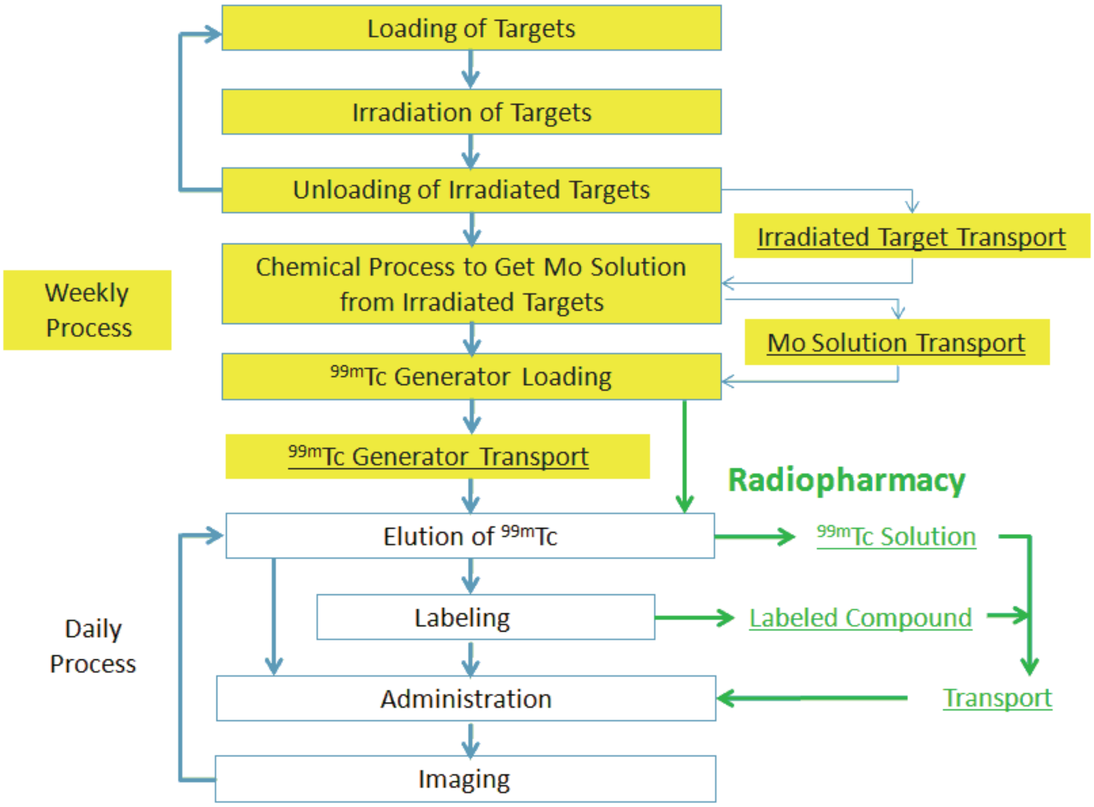


Figure 2. Flow diagram of fission Mo

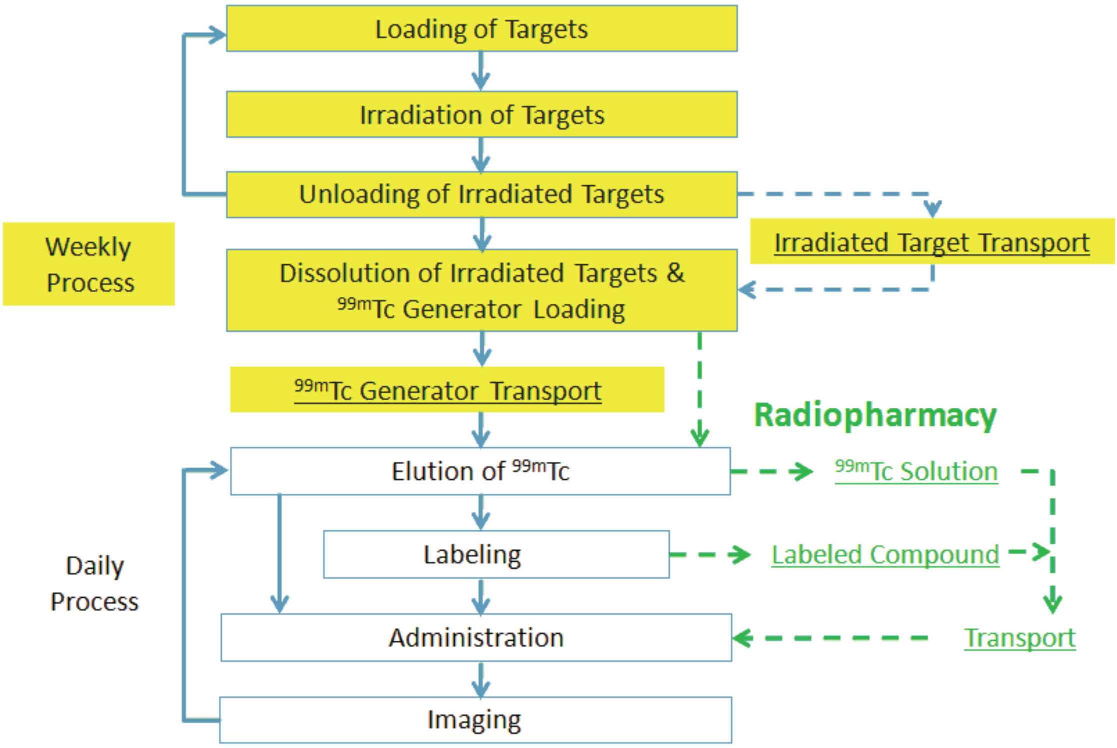


Figure 3. Flow diagram of (n,γ)^{99}Mo by ^{99m}Tc generators

(Dot path: potential scheme in the future)

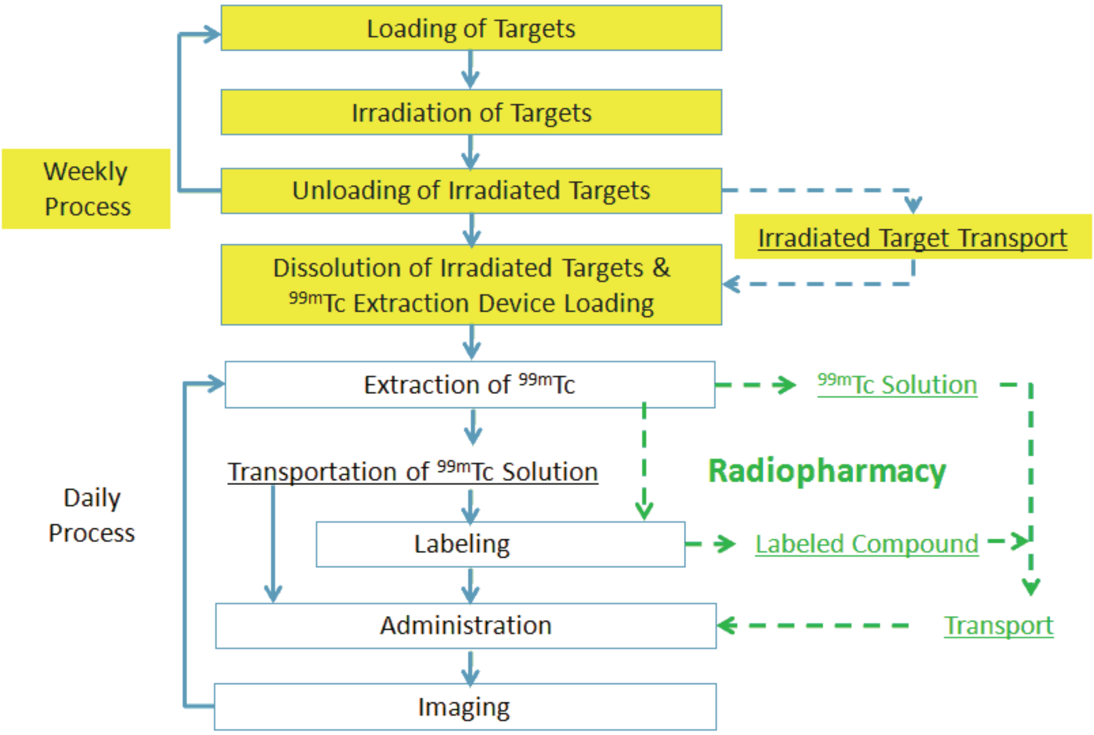


Figure 4. Flow diagram of (n,γ)^{99}Mo by ^{99m}Tc extraction device

(Dot path: potential scheme in the future)

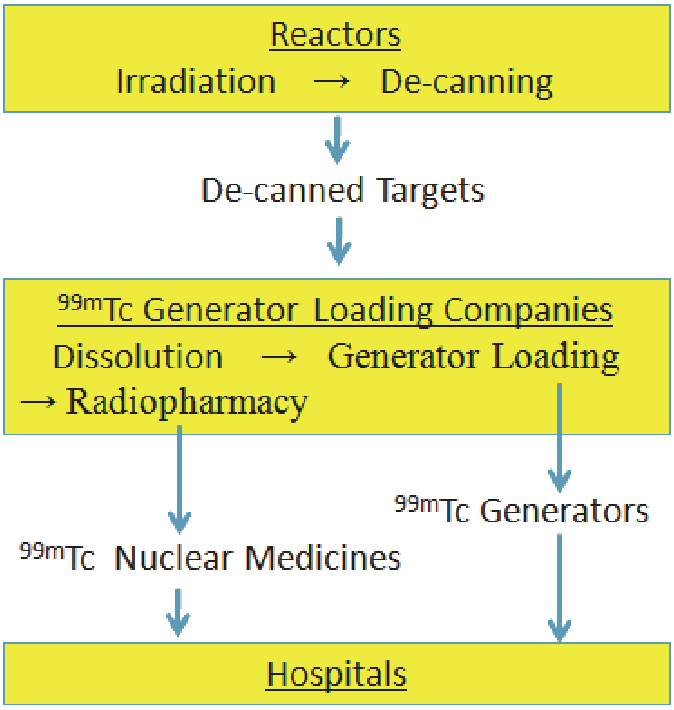


Figure 5. Regional mass (n,γ)^{99}Mo supply scheme

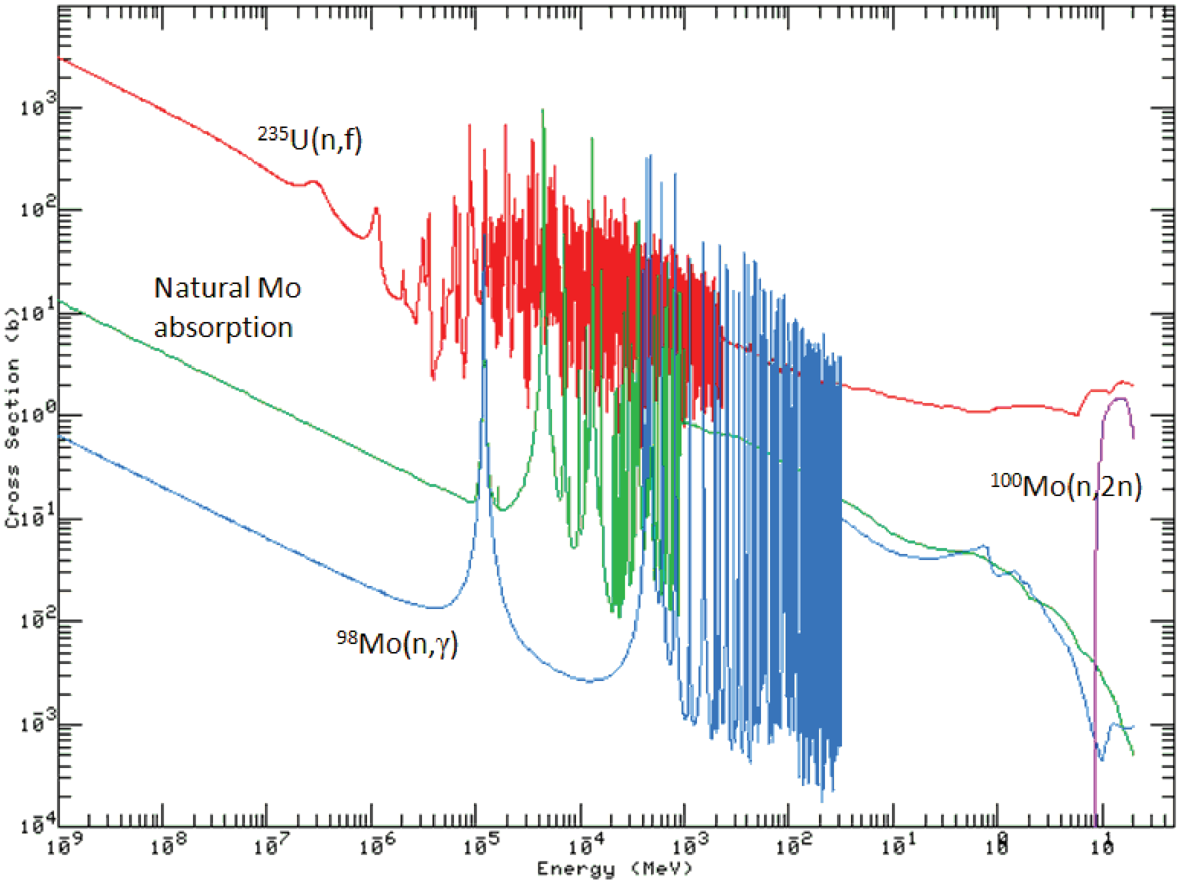


Figure 6. Energy dependent cross sections of ^{98}Mo(n,γ), ^{100}Mo(n,2n), natural Mo total neutron absorption and ^{235}U(n,f)

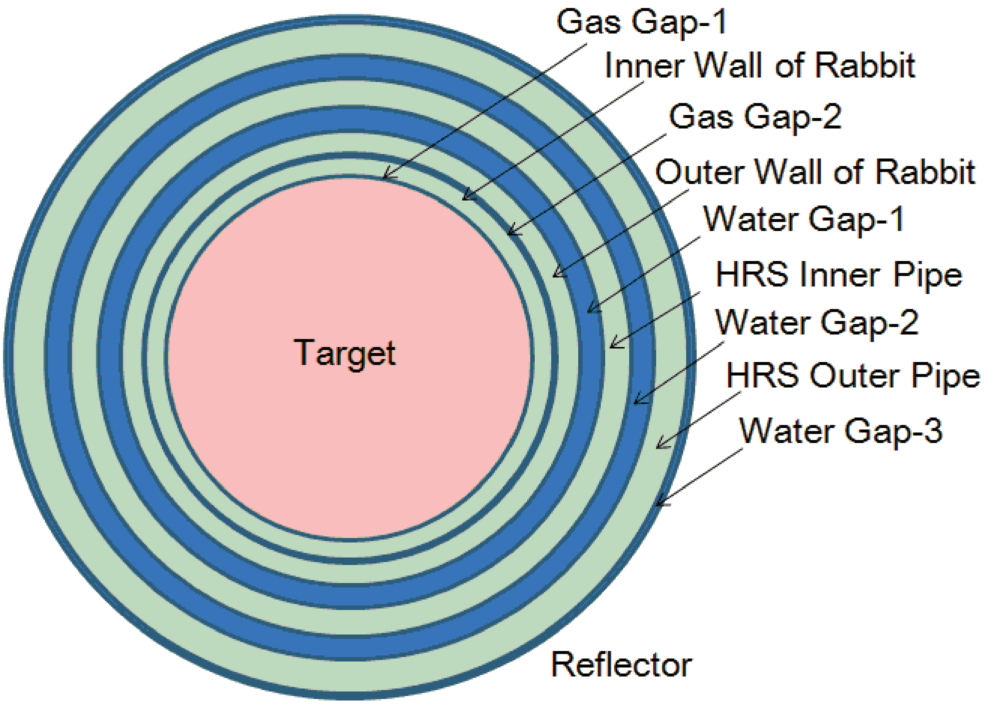


Figure 7. Conceptual cut view of hydraulic rabbit system irradiation part

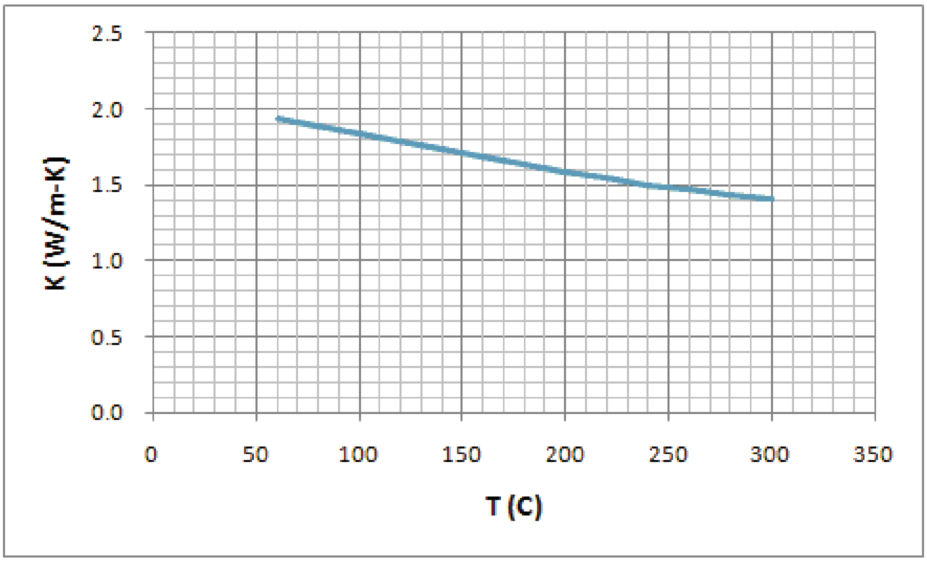


Figure 8. Conductivity of 3.28 g/cm^3 MoO^3 pellet for 60 ~ 300 °C range

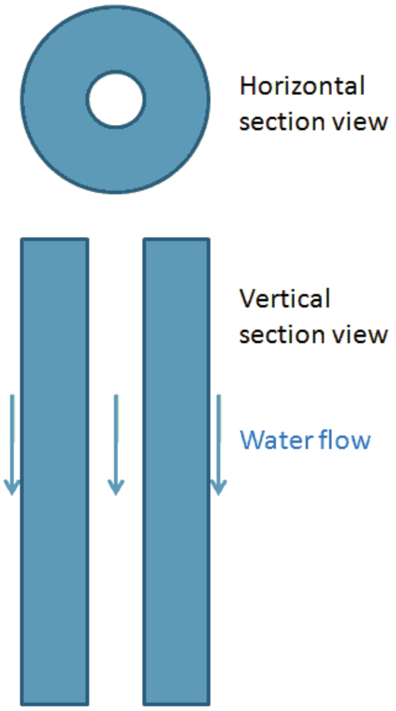


Figure 9. Conceptual view of an annular target

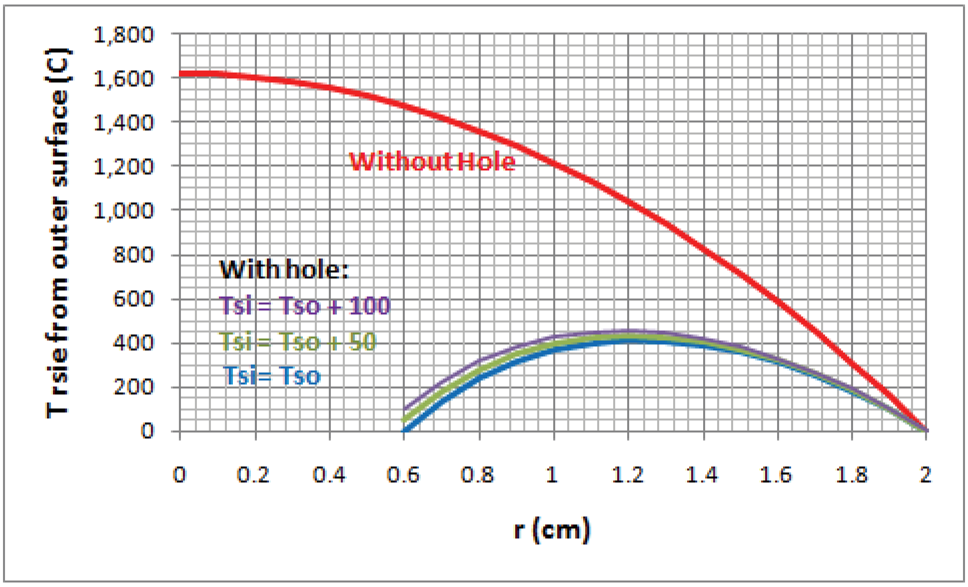
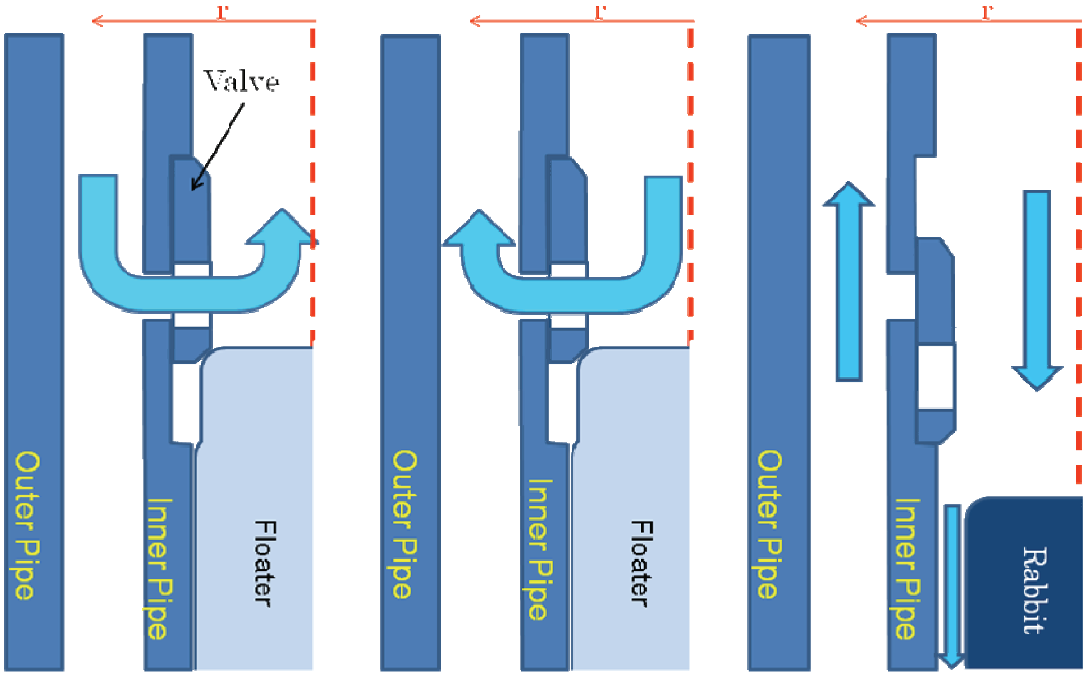


Figure 10. Pellet temperature rise from outer surface temperature



(a) After rabbit unloading (b) Just before rabbit loading (c) After rabbit loading

Figure 11. Concept to replace rabbits by a void aluminum can when rabbits are unloaded

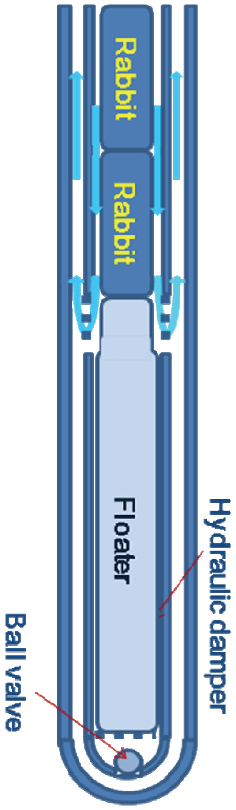


Figure 12. Conceptual view of floater during irradiation of rabbits

APPENDICES

A.1 Status of global ^{99}Mo supply

A.1.1 History of ^{99}Mo production and supply

Among notes of Cristina Hansell [1] on the history of ^{99}Mo production in USA, some are picked up here. "The ^{99}Mo was initially produced by the US AEC (Atomic Energy Commission) at the Brookhaven and Oakridge National Laboratories, and by 1966 commercial enterprises took over the production and distribution. AECL in Canada began to produce ^{99}Mo at the NRU on May 1, 1970 and then at the NRX on May 1, 1971. Reactors used for ^{99}Mo production in USA were closed in 1977 and 1990. In 1990, the US Congress had established the Isotope Production and Distribution Program (IPDP), combining all DOE isotope production activities. In 1992, the NRX was closed and the NRU became the sole reactor for the ^{99}Mo production in North America. Plans to use Omega West reactor at Los Alamos National Laboratory (LANL) were initiated to supply about 30% US market from 1993. DOE bought the Cintichem technology, and $3.5M was invested for process development at the LANL. However, a leaking coolant pipe was discovered in December 1992 and the reactor was shut down. In 1996, the Annular Core Research Reactor (ACRR) at the Sandia National Laboratory was identified as an alternative ^{99}Mo producer to supply 100 % US market while the reactor is in operation. The ACRR was converted for the ^{99}Mo production and modifications to its associated hot cell facilities were nearly completed, but production never started. Because US radioisotope users already made long-term contracts with other suppliers, so the commercial success of the ACRR seemed quite doubtful. The IPDP requires self-sustainability of the reactor."

In early 1980's, AECL began a project to build two MAPLE reactors dedicated for isotope production, to replace the ^{99}Mo production at NRU and to cover world demand by alternating operation of the two reactors. The project was halted in 1992 when majority of reactor structures were completed. After then the project resumed in 1996 and commissioning of MAPLE-1 started in 2000. After long time for the commissioning due to some regulatory issues, in May 2008, the AECL announced stopping of the MAPLE project. The reactors did not reach their designed full power 10 MW nor isotope produced. AECL also announced its intention to seek an additional five-year extension of the operating license for NRU from 2011 to 2016 to maintain production of ^{99}Mo for the intermediate term.

As IRE began supply of ^{99}Mo from 1979 [2] using HFR, BR2 and OSIRIS, the production of ^{99}Mo in Europe would be initiated around that time. The ^{99}Mo production facility of South Africa using SAFARI was commissioned in 1993 [3]. Then the five reactors – NRU, HFR, BR2, OSIRIS and SAFARI, became primary reactors producing ^{99}Mo.

In Japan, JAERI studied fission Mo production using enriched uranium from 1972 to 1977 by producing 10 ~ 20 Ci per each test, and after then $(n,\gamma)^{99}$Mo production until 1985 [4]. But commercial production has never been done.

In Korea, (n,γ)^{99}Mo was produced in TRIGA Mk-III and HANARO for supply of ^{99m}Tc solution. There have been studies on fission Mo including participation in a Coordinated Research Project (CRP) of IAEA on ^{99}Mo production using LEU or neutron activation [5] but none has been actually produced. More details are described in another JAEA report [6].

A.1.2 Status of ^{99}Mo supply

As shown in Table A.1-1, majority of world ^{99}Mo has been produced by the five aged reactors. Their peak production capability is about 250% of world demand. It is noticeable that the top three reactors – NRU, HFR and SAFARI, had shown excellent availability. There are many reactors in the category of 'others' in the table – ORPHEE in France, FRJ-2 and FRM-2 in Germany, OPAL in Australia, RSG-GAS in Indonesia, RA-3 in Argentina, LVR-15 in Czech, HFETR, MJTR and SPR in China, several reactors in Russia, etc., however, their total market sharing is small.

The HEU has been used for the targets at all primary ^{99}Mo production reactors. It seems that the first conversion to LEU targets among them will be SAFARI. The conversion in 2010 [7] following the full conversion of SAFARI fuel in June 2009 is expected. LEU targets are used in OPAL. ANSTO produced ^{99}Mo for 25 years by irradiating 1.8 ~ 2.2% LEU pellets in the HIFAR. Its processing facility was shut down in 2007 to convert to an expanded ^{99}Mo production process that utilizes 19.75% LEU targets at OPAL. It was foreseen [8] that ANSTO will become one of global ^{99}Mo suppliers. CNEA began ^{99}Mo production using HEU targets at RA-3 in 1985. They developed LEU-based production technology and converted to LEU in 2002. Their LEU target processing technology was transferred to ANSTO [8]. The Karpov Institute of Physical Chemistry in Russia, is producing ^{99}Mo by irradiating HEU targets for domestic use since 1985. The institute supplies ^{99m}Tc generators to over 200 hospitals and clinics in the country [8]. USA supplied HEU together with Cintichem technology to Indonesia, but the supply of HEU was stopped. Since HEU stock in Indonesia is almost used up recently, LEU must be used in the RSG-GAS, as well. (n,γ)^{99}Mo at HFETR and MJTR, and HEU fission Mo at SPR and HWRR were produced for domestic use in China. The HWRR was shut down at the end of 2007 and the CARR will replace the HWRR with much large production capability.

There are new reactor projects in which ^{99}Mo production is included. In Europe, three new research reactor projects to replace OSIRIS, HFR and BR2 are ongoing. The first runner JHR is a 100 MW material test reactor under construction from 2006 with a planned operation from 2014. PALLAS was under international bidding but it was recently halted. However, Dutch Government expressed that they support the project. The PALLAS is intending to have more than 100% peak production capability to satisfy future world demand. MYRRHA has been under conceptual design. In March 2010, the Belgian Government [9] approved a project toward the MYRRHA. They are hoping to start construction in 2015 and begin the first phase of operation in 2023. JHR and MYRRHA would function as backup reactors of PALLAS in ^{99}Mo production, if all projects for the three reactors are successfully implemented. CARR in China reached initial criticality on 13 May 2010. It seems that Canada is thinking about construction of a new 20MW Canadian Neutron Source [10] for the supply of medical isotopes and neutron beam applications against the planned final shutdown of the NRU in 2016.

A.1.3 Recent shortage in ^{99}Mo supply

Although there are many reactors producing ^{99}Mo as mentioned in the previous section, long term unexpected outage of primary reactors in the Table A.1-1 has been causing global shortage in ^{99}Mo supply.

In the fall of 2007 when the NRU was shut down for maintenance, Canadian Nuclear Safety Commission (CNSC) denied permission for its restart due to a dispute over the installation of an independent power supply system for emergency core cooling pumps, which was one of regulatory mandates for the extended operation of NRU to 2011. This caused a shortage of ^{99}Mo and the Canadian Government intervened to order the reactor restarted. The NRU restarted in December 2007, but the operation ceased from May 2009 due to a leak of heavy water in the reactor vessel. Subsequently, multiple points of corrosion were identified in the reactor vessel, and the AECL postponed restart of NRU a few times. The NRU restarted on 17 August 2010. Present operation license of NRU is until 2011 with anticipated extension to 2016.

In August 2008, a small leak in the primary cooling pipe embedded in the reactor pool concrete was found in the HFR. The leak was not repaired but the Duch Government allowed restart in February 2009 with a condition that the leak will be repaired early 2010. The HFR shut downed on 19 February 2010, and they expect about 6 month’s outage for the repair.

While the HFR was shutdown in 2008, an environmental release of ^{131}I occurred from an isotope production facility of IRE, which caused two months outage of BR2.

In November 2007, armed attackers approached the facilities of SAFARI [1], which was second reported breach at the site in the past couple of years. It did not impact to the production of ^{99}Mo, but worry on the potential unavailability of ^{99m}Tc prevails.

A.1.4 Responses against the ^{99}Mo shortage

For an urgent action against the long term shutdown of HFR from 19 February 2010, operation schedules of BR2 and OSIRIS were adjusted to minimize the impact from the long term shutdown of the HFR, and Maria in Poland initiated irradiation of fission Mo targets. Meanwhile, it is generally perceived that aging of primary reactors is the root cause of current shortage and the situation will become worse as time going on, unless new productions are available. Ways to create the new productions can be categorized into utilization of existing reactors and development of new production technologies.

On June 15, 2009, MDS Nordion agreed to study the feasibility of the Karpov Institute providing the company supply of ^{99}Mo for the global nuclear medicine market. The Karpov Institute has been supplying about 90% of ^{99}Mo and ^{99m}Tc generators in the Russian market covering more than 200 clinics. Missouri University has been studying ^{99}Mo production at MURR using LEU targets and Cintichem process. They expect about 50% domestic supply from 2012 [11]. FRM-II is seeking funding to upgrade the facility to produce ^{99}Mo. They expect almost enough ^{99}Mo production in five years by using HEU targets with a peak production capability covering all demand in Europe [12]. JAEA and KAERI are studying (n,γ)^{99}Mo at JMTR and HANARO, respectively.

In January 2009, Babcock & Wilcox (B&W) announced that they made a contract with Covidien for the supply of about a half of US demand in ^{99}Mo if they succeed in the development of new reactor and ^{99}Mo separation technologies. The concept is direct extraction of Mo from LEU solution fuel from 100 ~ 200 kW solution fueled reactors. A task force team of Canada [13] studied new methods of ^{99}Mo and recommended a photo-fission method using ^{238}U targets. In April 2009, MDS-Nordion contracted with TRIUMF (Tri-University Meson Facility) for a feasibility study on this method. A few days after above contract with TRIUMF, Positron Systems Inc. and Idaho State University announced that they developed a new method producing short lived isotopes using an accelerator and they are studying about supply of ^{99}Mo produced at Idaho accelerator to US market. Details are not disclosed.

B. Wolterbeek of Delft University applied a patent for a new ^{98}Mo(n,γ) method using neutrons from other than reactors. The news [14] described that the energy transfer involved separates the water-soluble ^{99}Mo from the surrounding atoms. Details are not disclosed.

In November 2009, USA passed the American Medical Isotopes Production Act of 2009 [15] and authorized a $163M program to work with industry for the production of ^{99}Mo without HEU. The goal is to accelerate the efforts to produce in adequate quantities for the needs of the U.S. medical community by the end of 2013.

On 13 April 2010, four institutions in Europe operating research reactors (CEA, NRG, SCK・CEN and TUM) [15] announced a position paper on scenario for sustainable ^{99}Mo production in Europe. They expected that existing aged reactors - HFR, BR2, OSIRIS and MARIA will produce ^{99}Mo until their life-time, and that FRM-II, JHR, PALLAS and MYRRHA will take over the production of ^{99}Mo for its long term availability in Europe. They emphasized that, due to the short half-life of ^{99}Mo, the responsibility for efficient and secure supply is more local and, therefore, the facilities to produce ^{99}Mo for the medium-term European needs must be located in Europe. For this, the future network would further reduce the risks of supply chain disruption, by fostering technical compatibility in target design, in target processing and in transport container use.

World Nuclear News on 03 June 2010 [16] informed "*Canadian government issued a call for* *project proposals for medical isotopes supply program. The program, announced in the 2010 budget, will promote non-reactor-based technologies for the supply of medical isotopes over the medium- and long-term. The C$35 million ($34 million) in funding will be provided over two years to advance linear accelerator and cyclotron technologies for the production of technetium-99m.*" It seems that the program is to support aforementioned photo fission project of TRIUMF.

A.1.5 Observation

Though USA consumes about a half of world ^{99}Mo, they do not produce it after the shutdown of second ^{99}Mo production reactor in 1990. The importance of local ^{99}Mo production in the USA is emphasized and a legal framework is working to accelerate the local production of self sufficient ^{99}Mo. Research reactor operators in Europe also emphasized the importance of the local production, and a concerted research reactor program for the long term stable production of ^{99}Mo in Europe is under progress. For the case of East-Asian region of which ^{99}Mo demand is third after USA and Europe, no special region wise action against the recent shortage of ^{99}Mo is found. Japan and Korea who have been importing all ^{99}Mo from abroad are considering $(n,\gamma)^{99}$Mo production at JMTR and HANARO. On 12 March 2010, FNCA National Coordinators' meeting decided to discuss establishment of a regional radioisotope network. Active discussions on the long term stable ^{99}Mo supply in the region are desired.

References

[1] C. Hansel, Nuclear Medicine's double hazard – Imperiled treatment and the risk of terrorism, *Nonproliferation Review, Vol. 15, No. 2, July 2008.*

[2] F.N. von Hippel and L.H. Kahn, Feasibility of eliminating the use of highly enriched uranium in the production of medical radioisotopes, *Science and Global Security, 14: 151-162, 2006.*

[3] http://www.terrapinn.Com /2009/powerza/speakerList.stm, read on 9 December 2009

[4] S. Okane, et al, Private Communication, 1985.

[5] I.N. Goldman, et al., Fostering new sources of Mo-99 for international nuclear medicines needs – IAEA CRP on Mo-99 production using LEU or neutron activation, 2008 RERTR International Meeting, Oct. 5-9, Washington, DC.

[6] B.J. Jun, et al, Revaluation of ^{99}Mo production by (n,γ) method at HANARO, JAEA- Review 2010-032, July 2010.

[7] MEDIA RELEASE of NECSA on 29 June 2009.

[8] Medical Isotope Production Without Highly Enriched Uranium, Nuclear and Radiation Studies Board, Division of Earth and Life Studies, NATIONAL RESEARCH COUNCIL OF

THE NATIONAL ACADEMIES, THE NATIONAL ACADEMIES PRESS, Washington D.C. www.nap.edu, 2009

[9] World Nuclear News, Approval for Myhrra, 05 March 2010,

[10] Government of Saskatchewan, The Canadian Neutron Source: *Securing the Future of Medical Isotopes and Neutron Science In Canada,* Submission to the Natural Resources Canada, Expert Review Panel on Medical Isotope Production, July 31, 2009.

[11] http://dels.nas.edu/nrsb/presentations/ralphbutler.pdf, Ralph A. Butler and Alan R. Ketring, National Academy of Sciences: National Medical Isotope Production Study, Missouri Research Reactor Center, University of Missouri, read on 4 December 2009.

[12] http://medicalphysicsweb.org/cws/article/research/40089, Aug 13, 2009

[13] Making Medical Isotopes, Report of the Task Force on Alternatives for Medical-Isotope Production, TRIUMF, Univ. British Columbia, Advanced Applied Physics Solutions, Inc. with support from Natural Resources Canada.
http://www.nuclearsafety.gc.ca/pubs_catalogue/uploads/Report-vPREPUB.pdf

[14] New technique promises non-U medical isotopes, 16 September 2008,
http://www.world-nuclear- news.org/

[15] Position paper by CEA, NRG, SCK•CEN & TUM, Scenario for sustainable molybdenum-99 production in Europe, 13 April 2010,
http://www.nea.fr/med-radio/docs/Multisources%20Mo-99%20production%20scenario%20for%20Europe%20%20Position%20paper-CEA-NRG-TUM-SCK%20CEN.pdf

[16] World Nuclear News, Steps to bolster isotope production, 03 June 2010.

Table A.1-1 Reactors supplying ^{99}Mo [2]

Reactor	Initial Operation	Availability (%)	Distributer	Avg./Peak Production (% World Demand)
NRU	1957	86	MDS-Nordion	40/80
HFR	1961	79	TYCO/IRE	30/50
SAFARI	1965	86	NTP	10/45
BR2	1961	31	TYCO/IRE	9/35
OSIRIS	1964	60	IRE	3/20
Others	-	-	Others	5/10
Total				100/250

A.2 Variation of ^{99}Mo and ^{99m}Tc activities and ^{99m}Tc portion in Tc

A.2.1 Derivation of equations

This section derives equations to calculate nucleus numbers of ^{99}Mo, ^{99m}Tc and ^{99}Tc in the irradiation targets, ^{99m}Tc generators and eluates. The equations can be used not only for solid target irradiation but also liquid irradiation regardless by fission or (n,γ).

While the ^{99}Mo production rate R either by ^{98}Mo(n,γ) or fission is a constant, the balance equation and its solutions for ^{99}Mo in the irradiation target are

$$\frac{dn^{Mo}}{dt} = R - \lambda^{Mo} n^{Mo} \tag{1}$$

$$n^{Mo} = \frac{R}{\lambda^{Mo}}(1 - e^{-\lambda^{Mo} t}) + n_p^{Mo} e^{-\lambda^{Mo} t} \tag{2}$$

$$A^{Mo} = \lambda^{Mo} n^{Mo} \tag{3}$$

where, n^{Mo}, A^{Mo} = number of nucleus and activity of ^{99}Mo, respectively, in the target at current time step,

n_p^{Mo} = number of ^{99}Mo nucleus in the target at initial or previous time step,

λ^{Mo} = decay constant of ^{99}Mo, and

t = time difference between previous and current time step.

The balance equation and its solution for the ^{99m}Tc in the irradiation target are

$$\frac{dn^{Tcm}}{dt} = y^{Tcm} A^{Mo} - \lambda^{Tcm} n^{Tcm} \tag{4}$$

$$n^{Tcm} = n_p^{Tcm} e^{-\lambda^{Tcm} t} + \frac{y^{Tcm} \lambda^{Mo}}{\lambda^{Tcm}(\lambda^{Tcm} - \lambda^{Mo})}[\lambda^{Tcm} n^{Mo} - R + (R - \lambda^{Tcm} n_p^{Mo}) e^{-\lambda^{Tcm} t}] \tag{5}$$

$$A^{Tcm} = \lambda^{Tcm} n^{Tcm} \tag{6}$$

where, n^{Tcm}, A^{Tcm} = number of nucleus and activity of ^{99m}Tc, respectively, in the target at current time step,

n_p^{Tcm} = number of ^{99m}Tc nucleus in the target at previous time step,

λ^{Tcm} = decay constant of ^{99m}Tc, and

y^{Tcm} = decay yield of ^{99}Mo to ^{99m}Tc.

The ^{99}Tc is a final product of ^{99}Mo and ^{99m}Tc in the equations. Its β-decay to ^{99}Ru is neglected due to 2.13E5 y half-life. Then, a difference between initial and current numbers of ^{99}Mo and ^{99m}Tc nuclei plus the production of ^{99}Mo during time interval t becomes the production of ^{99}Tc.

$$n^{Tc} = n_p^{Tc} + n_p^{Mo} + n_p^{Tcm} + Rt - n^{Mo} - n^{Tcm} \tag{7}$$

where, n^{Tc}, n_p^{Tc} = number of ^{99}Tc nucleus in the target at current and previous time steps, respectively.

Above equations can be applied to other situations such as the target outside of irradiation site, ^{99m}Tc generators and ^{99m}Tc solutions by giving a zero reaction rate and appropriate initial values. For the target outside of irradiation site and for the ^{99m}Tc generators, Eq.s (2), (5) and (7) are simplified by the zero reaction rate.

$$n^{Mo} = n_p^{Mo} e^{-\lambda^{Mo} t} \tag{2-0}$$

$$n^{Tcm} = n_p^{Tcm} e^{-\lambda^{Tcm} t} + \frac{y^{Tcm} \lambda^{Mo}}{\lambda^{Tcm} - \lambda^{Mo}} (n^{Mo} - n_p^{Mo} e^{-\lambda^{Tcm} t}) \tag{5-0}$$

$$n^{Tc} = n_p^{Tc} + n_p^{Mo} + n_p^{Tcm} - n^{Mo} - n^{Tcm} \tag{7-0}$$

In a ^{99m}Tc solution, above equations are further simplified by neglecting the content of ^{99}Mo.

$$n^{Tcm} = n_p^{Tcm} e^{-\lambda^{Tcm} t} \tag{5-1}$$

$$n^{Tc} = n_p^{Tc} + n_p^{Tcm} - n^{Tcm} \tag{7-1}$$

A.2.2 Solution irradiation for daily extraction of ^{99m}Tc

For the irradiation of solution for daily extraction of ^{99m}Tc, a solution irradiation loop is needed. If chemical treatment of the solution or cooling of the target in addition to the heat transfer in the irradiation site is needed, a quick daily circulation would not be enough and a continuous circulation of the solution is needed. In this case, the target decays without production when it is at the outside of the flux zone, which may give a certain impact to the production quantity and quality of ^{99m}Tc. The calculations are carried out to find out this impact as well as to compare with weekly ^{99}Mo supply for ^{99m}Tc generators.

All calculations are normalized to the total production rate of ^{99}Mo in the irradiation system. Efficiencies for the extraction of Tc elements from the solution target, Mo loading to the ^{99m}Tc generators and elution from the ^{99m}Tc generators, are assumed as 0.9.

(1) No continuous circulation

For this calculation, the time required for the daily circulation to extract ^{99}Tcm is supposed sufficiently short and neglected. Figure A.2-1 shows a result of the calculation. After sufficiently long shutdown to neglect any ^{99}Mo remained in the target, the reactor starts operation at time 0. The daily extraction of ^{99m}Tc starts from one day after reactor startup. The reactor operation stops after the target activity is sufficiently saturated (576 h in the figure). After seven days shutdown, the reactor operation starts again.

If the same reactor operation pattern is iterated, the pattern shown in the second figure in Figure A.2-1 is iterated. If the reactor stops operation in the Sunday morning, the target in the system can be used as if it is a ^{99m}Tc generator for the next week while the reactor is shutdown.

Restart of the reactor from the next Sunday morning enables continued supply of Tc-99m. Therefore, regular one week shutdown of the reactor for refueling would not interrupt the continued supply of ^{99m}Tc.

(2) Continuous circulation of target

If the cooling of the solution target by natural heat transfer in the irradiation site is not sufficient, a continuous circulation of the target is needed to cool the target at outside of the flux region. If the circulation is very slow, it does not help the target cooling. Therefore, the circulation time must be much shorter than the half-life of ^{99m}Tc. As the circulation reduces net irradiation time for unit volume of target and total decay time of the target in a day would not be so short compared to the half-life of ^{99m}Tc, the production quantity and quality of ^{99m}Tc may be affected by the circulation speed as well as the volume ratio of outside irradiation site. However, calculations for various circulation speeds and volume ratios resulted in almost exactly the same values as shown in Figure A.2-1. It would be understood as following way:

When the target irradiation time is T and the target spends τ after irradiation until it enters into the irradiation site again, Eq.s (2), (5) and (7) at T become initial values of Eq.s (2-0), (5-0) and (7-0), and Eq.s (2-0), (5-0) and (7-0) at τ become values at the next entrance into the irradiation site. For the case of ^{99}Mo activity, the relation is expressed as

$$A_j^{Mo} = [R - (R - A_{j-1}^{Mo})e^{-\lambda^{Mo}\mathrm{T}}]e^{-\lambda^{Mo}\tau} \tag{6-1}$$

where, A_j^{Mo}, A_{j-1}^{Mo} = activities of ^{99}Mo in the target when it enters into the irradiation site j th and (j-1)th times, respectively, and

T, τ = resident durations of the target in and outside of irradiation site, respectively.

Eq. (6-1) is a relationship of A_j^{Mo} series and can be expressed with an initial term.

$$A_j^{Mo} = \frac{R(e^{-\lambda^{Mo}\tau} - e^{-\lambda^{Mo}(\mathrm{T}+\tau)})(1 - e^{-\lambda^{Mo}j(\mathrm{T}+\tau)})}{1 - e^{-\lambda^{Mo}(\mathrm{T}+\tau)}} + e^{-\lambda^{Mo}j(\mathrm{T}+\tau)}A_0^{Mo} \tag{6-2}$$

where, A_0^{Mo} = initial activity of ^{99}Mo in the target (j = 0, when reactor starts operation).

To compare above with the activity of ^{99}Mo without circulation which is expressed in Eq. (3), the value without circulation at $t = j(\mathrm{T} + \tau)$ is expressed as B_j^{Mo} here.

$$B_j^{Mo} = R(1 - e^{-\lambda^{Mo}j(\mathrm{T}+\tau)}) + A_p^{Mo}e^{-\lambda^{Mo}j(\mathrm{T}+\tau)} \tag{6-3}$$

Then, the relation between A_j^{Mo} and B_j^{Mo} is expressed as

$$A_j^{Mo} = \frac{e^{-\lambda^{Mo}\tau} - e^{-\lambda^{Mo}(\mathrm{T}+\tau)}}{1 - e^{-\lambda^{Mo}(\mathrm{T}+\tau)}}B_j^{Mo} + \frac{1 - e^{-\lambda^{Mo}\tau}}{1 - e^{-\lambda^{Mo}(\mathrm{T}+\tau)}}A_0^{Mo}e^{-\lambda^{Mo}j(\mathrm{T}+\tau)} \tag{6-4}$$

As the circulation time (T + τ) is much shorter than the half-life of ^{99}Mo, $\lambda^{Mo}(\mathrm{T} + \tau)$ is much smaller than 1 and Eq. (6-4) can be approximated as Eq. (6-5) with sufficient accuracy.

$$A_j^{Mo} \cong \frac{\mathrm{T}}{\mathrm{T}+\tau}\left(B_j^{Mo} + A_0^{Mo} e^{-\lambda^{Mo} j(\mathrm{T}+\tau)}\right) \tag{6-5}$$

In case of zero initial value or after sufficient irradiation time, the ratio becomes the volume ratio of outside flux zone in the total loop volume. As above equations are for unit volume, the total activity of ^{99}Mo in the loop is a multiplication of loop volume to above values. And as the volume ratio of irradiation site is the same with the ratio of time duration in the irradiation site, Eq. (6-5) indicates that the loop total activity of ^{99}Mo is almost neither dependent on the circulation time nor the loop volume.

The derivation of Eq. (6-5) is lengthy, but it can be easily guessed that the activity of target is almost proportional to its portion of irradiation time. The equations for ^{99m}Tc and Tc are very complicated, but they can be heuristically explained. As ^{99m}Tc is produced by ^{99}Mo, its activity is determined by the variation of ^{99}Mo. The variation of ^{99}Mo with circulation is almost the same with that without circulation as aforementioned. Therefore, total ^{99m}Tc activity in the circulating loop is also the same as in the fixed target only in the irradiation site. It is explained the same way for the Tc.

A.2.3 Weekly irradiation for ^{99m}Tc generators

When targets are irradiated for weekly supply of ^{99}Mo for the ^{99m}Tc generators, following scenario is assumed for calculation: The targets are replaced once a week. Since the replacement of (n,γ) targets are very simple, the time needed for the replacement is neglected. The Mo solution is loaded into ^{99m}Tc generators. A 10% loss of Mo (efficiency 0.9) is assumed for the generator loading. The ^{99m}Tc generators are eluted before shipment - after 6 hours from the target replacement. The first elution of ^{99m}Tc generators by a radiopharmacy or hospital is after 24 hours from the target replacement, and then daily elution is iterated during every weekday. The 90% efficiency is assumed for every elution.

Figure A.2-2 is a result of the calculation. The ^{99}Mo is not available during the first week after reactor startup and then an identical pattern is iterated. Available ^{99m}Tc activity just after the elution is about 48 % of ^{99}Mo saturation activity on the first weekday (Monday) and about 19% on the last weekday (Friday). Just after elution, the portion of ^{99m}Tc in the total Tc is about 25% when the generator is eluted every 24 hours.

A.2.4 Comparison of available ^{99m}Tc between direct extraction from solution target and elution of ^{99m}Tc generator

When we compare the available ^{99m}Tc activities, first of all, a time needed for the delivery of ^{99m}Tc from the reactor to hospitals or radiopharmacies becomes very important factor. The ^{99m}Tc activities in the eluate shown in Figure A.2-2 are actual activities available to ^{99m}Tc generator users. But those shown in Figure A.2-1 are values after extraction at the reactor. As the ^{99m}Tc decays during the delivery, its activity available for actual use becomes lower as the delivery time is longer. The delivery time includes time for the process to extract the ^{99m}Tc, packaging, inspection for radioactive material transportation, transportation, inspection for acceptance by the user, and setting for use. Figure A.2-3 compares available ^{99m}Tc when five-hours are assumed for the delivery time. As shown in the figure, the available ^{99m}Tc and its portion in the total Tc are significantly reduced due to its decay during the delivery.

The requirement on the ^{99m}Tc portion is not clear. If a similar portion with that of ^{99m}Tc generator is required, it can be increased by cleaning up Tc elements in between daily extraction of ^{99m}Tc. The cleanup of Tc elements is actually the same process as the extraction of ^{99m}Tc. Figure A.2-4 shows a case with cleanup; the Tc elements are cleaned up after 10 hours from the daily ^{99m}Tc extraction and four hours for the delivery time is assumed. The portion of ^{99m}Tc is similar with that of ^{99m}Tc generator. Even though the time for accumulation of ^{99m}Tc is reduced to 14 h due to the cleanup, the available ^{99m}Tc is only slightly reduced due to one hour reduction in delivery time.

A.2.5 Effect of elution interval

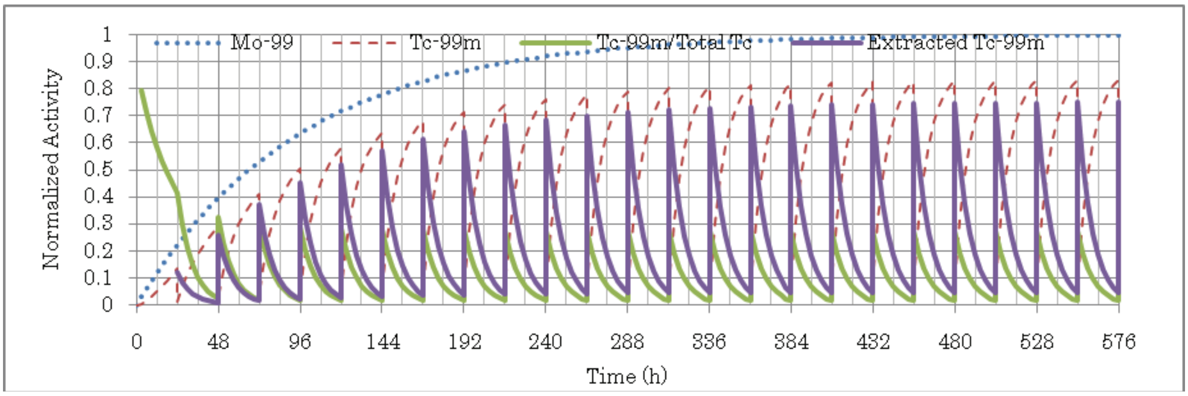
Figure A.2-5 shows an example of relative activity variations for a ^{99m}Tc generator and its eluate. The scenario is not based on an actual practice but made for the convenience's sake to understand the effect of elution interval: The generator is fully eluted at time 0 (say 09:00 Saturday) by its supplier and then shipped. Its first elution in the week is at 48 h (say 09:00 on Monday) and it is basically eluted once every 24 h during the weekdays. From the third weekday (Wednesday), it is eluted once more at 4 h after the first elution of the day (say 13:00). An efficiency of 90 % is assumed for every elution on the weekday.

During the initial two days, the ^{99m}Tc activity in the generator reaches a maximum value at $ln(\lambda^{Tcm}/\lambda^{Mo})/(\lambda^{Tcm} - \lambda^{Mo})$ (= 22.84 h) and then decreases approaching a transient equilibrium. It indicates that elution of the generator at every 24 h gives almost maximum ^{99m}Tc activity available. Meanwhile the portion of ^{99m}Tc in Tc decreases continuously due to an accumulation of the Tc. In this scenario, the portion of ^{99m}Tc at the first elution is only 13.5 %. In the eluate, there is no more ^{99m}Tc production. Therefore, the ^{99m}Tc portion decreases faster than in the generator. For some cold kit, the supplier specifies that the generator must be eluted within 24 hours prior to obtaining any eluate for labeling as explained in Section 3.1 of main text. If this cold kit is used on the first working day, the generator should be eluted within 24 h prior to the first elution.

In a case the generator is eluted only once every 24 h, a pattern similar with second weekday (Tuesday) in the figure is iterated with a daily decrement of available ^{99m}Tc along with the decay of ^{99}Mo. That is, the variation of ^{99m}Tc portion in the eluate is identical every day but the activity of ^{99m}Tc in the eluate daily decreases. If it is assumed that the ^{99m}Tc eluted at 09:00 is used for administration to patient at 11:00, total ^{99m}Tc activity available for the administration for five working days is about 1.28 Ci. If the activity of generator calibrated at 12:00 Wednesday is 1 Ci, then about 4 Ci ^{99m}Tc is available for the administration.

If the generator is eluted twice in a day, the pattern of fourth weekday (Thursday) in the figure is iterated. The twice elutions from the third weekday may be applied when the activity of generator is not enough during the later part of the week. The gains from the twice elutions in the figure compared to once elution are 41 % on the third weekday and 36 % on the fourth and fifth weekdays. The higher portion of ^{99m}Tc by the twice elutions, especially for the second eluates shown in the figure, is an additional advantage.

The activity of a ^{99m}Tc generator is expressed by the activity of ^{99}Mo at the calibration timing. Since the activity decreases with time the calibration time must be checked. The figure is the case that the generator is eluted by the generator supplier and calibrated at time 0 for shipment, and the ^{99m}Tc is eluted at 09:00 every weekday for medical diagnoses.



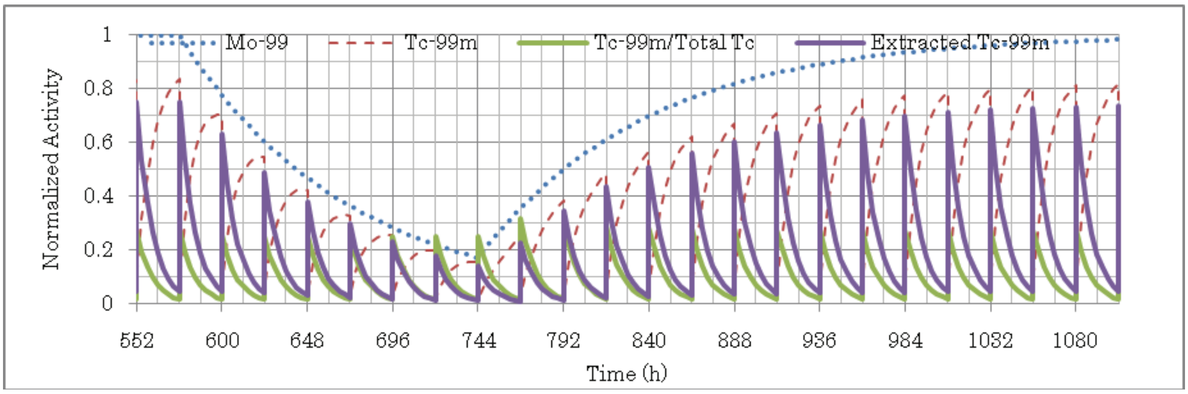


Figure A.2-1 ^{99}Mo and ^{99m}Tc activity, and ^{99m}Tc portion in Tc when the solution is quickly circulated only once per day for the extraction of ^{99m}Tc

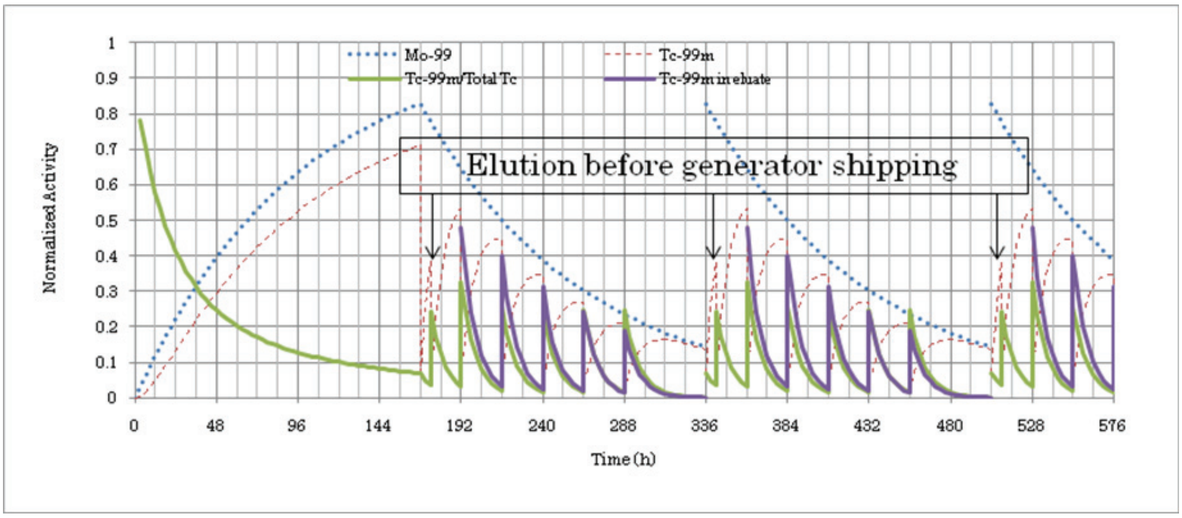


Figure A.2-2 ^{99}Mo and ^{99m}Tc activity, and ^{99m}Tc portion in Tc in the solid targets and ^{99m}Tc generators

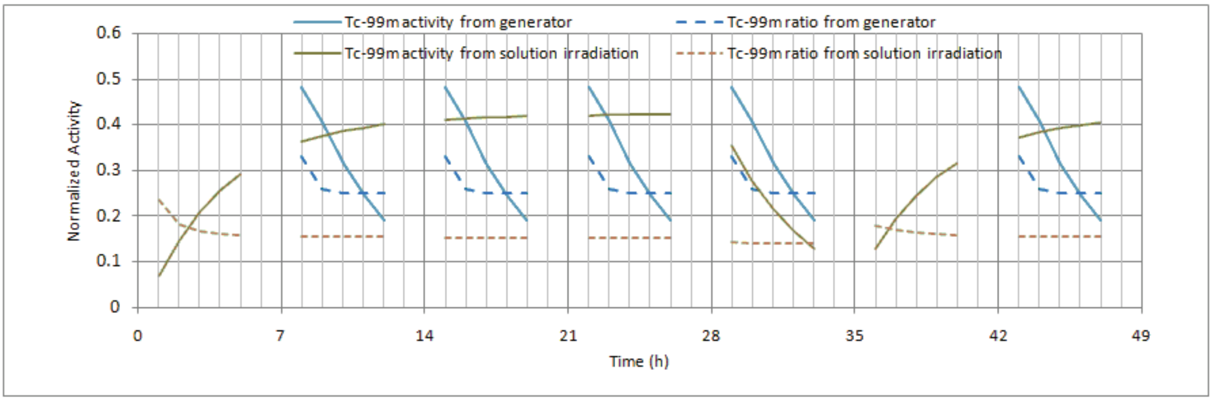


Figure A.2-3 Comparison of ^{99m}Tc availability without cleanup of Tc from the solution target (One extraction every day & 5 h delivery time for direct extraction of ^{99m}Tc)

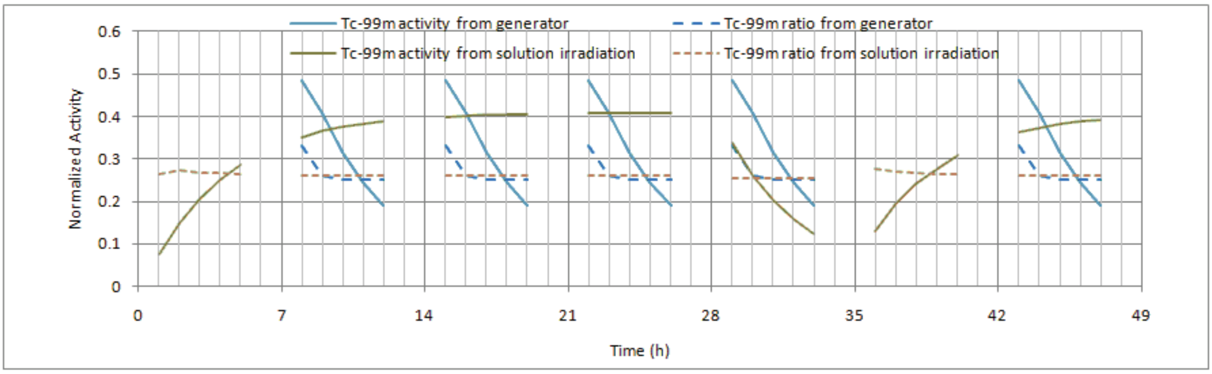


Figure A.2-4 Comparison of ^{99m}Tc availability with cleanup of Tc from the solution target (Cleanup of Tc 10 h after ^{99m}Tc extraction & 4 h delivery time)

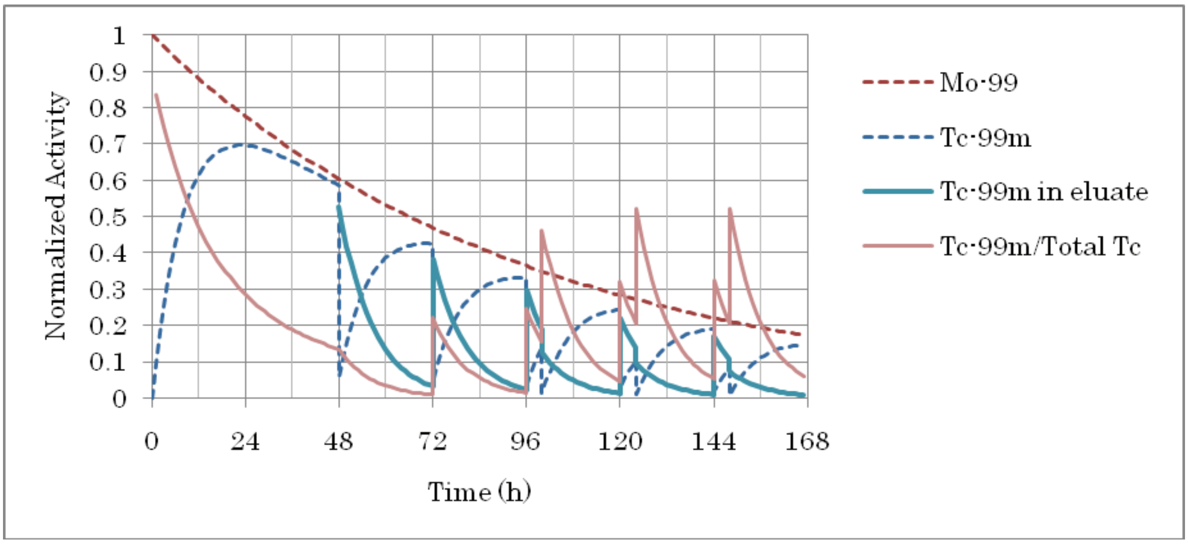


Figure A.2-5 An example of variations of activity and ^{99m}Tc portion in Tc for the ^{99m}Tc generator and its eluate showing effect of elution time interval

A.3 Assessment of activity and cost for the use of ^{99}Mo

A.3.1 Introduction

A good understanding on the ^{99}Mo demand and its cost is essential to judge whether the (n,γ)^{99}Mo production will be sufficient to satisfy the demand and whether its production cost will be reasonable. The demand is always expressed by its activity. While the ^{99}Mo decays with 66 h half-life, the time duration involved from its production to end of use are long enough to change its activity significantly. Therefore, a good understanding on the actual meaning of statistics on the demand is needed. But sometimes it is not clear. Next section explains relevant information and our opinion on this matter.

It is often said that, compared to fission Mo, the (n,γ)^{99}Mo has several advantages including much low production cost. However, users always choose the fission Mo as far as it is available. The only but critical shortage of (n,γ)^{99}Mo compared to fission Mo is its extremely low specific activity, which makes its use less convenient and perhaps requires the higher cost to use. Many efforts have been given to improve the convenience in the use of (n,γ)^{99}Mo, but it will be never as convenient as the use of fission Mo. Then we have to judge whether there is any possibility that users will choose the (n,γ)^{99}Mo. We say "Fission Mo has risk of nuclear proliferation, environmental release of fission products and instability in supply, and also produces much more radwaste. The (n,γ)^{99}Mo does not have such problems and may open the shortest way to overcome current shortage of ^{99}Mo. But it is a little less convenient in use." Then we need to figure out how much it will be actually less convenient. As the inconvenience may be represented by additional cost, we need to understand the cost to use the fission Mo first. Then we may find out how to go with the (n,γ)^{99}Mo. The cost to use the fission Mo is analyzed in Section A.3.3.

A.3.2 ^{99}Mo activity

The ^{99}Mo demand is usually expressed by six-day-Ci, but actually it is a unit used by ^{99}Mo suppliers when they sell the ^{99}Mo solution. They assure that the ^{99}Mo activity six days after it leaves their facilities will be at least the activity expressed by the six-day-Ci [1]. In the actual practice, a supplier usually determines the time leaving its facility at 12:00 local time of the facility. For the case of a ^{99m}Tc generator used for a working week from Monday to Friday for an example, the ^{99}Mo solution must leave the supplier's facility in the previous week. If it is on Thursday and then if the ^{99m}Tc generators are loaded on Friday, middle of the working week (12:00 Wednesday) becomes the sixth day after the shipping of ^{99}Mo solution. Then the activity by six-day-Ci can represents the activity while the ^{99}Mo is under use by the end users, and thereby it may be considered as the actual demand.

However, above is reasonable only when the facilities for ^{99}Mo solution supply, ^{99m}Tc generator loading and its use are within reasonable distances between them. For the cases of Japan and Korea who import all of their ^{99}Mo solution from North America, Europe and South Africa, the ^{99}Mo solution leaving a supplier's facility on Thursday local time cannot be used for the ^{99m}Tc generator loading on Friday. If they work during weekend, the generators may be available to users from next Monday. But it seems that the practice has not been such a way. It also seems that the ^{99}Mo solution suppliers usually ship twice a week. As replacement of uranium targets in a reactor and its post processing are complicated, shipping everyday may not be practical. Then the interval for the next shipping is three or four days, which results in additional three or four days decay of the ^{99}Mo solution delivered to Japan and Korea.

It is clear that Japan and Korea must buy much more ^{99}Mo solution than USA to use an identical amount of ^{99}Mo. It also requires the higher air transport fee not only for the longer distance but also for the heavier cask due to the higher activity for transportation. Then, the unit cost of ^{99}Mo solution for use in Japan and Korea must be much higher than USA.

The activity of a ^{99m}Tc generator is expressed by different ways depending on its supplier, such as the activity when the generator is manufactured, on the first day of generator usage, on the third day of generator usage, etc. For the case of the 500 Ci Master milkers in Japan loaded on Friday for their usage during next week, the activity is calibrated at 12:00 Friday – on the day of manufacture. Since the information is very specific, it allows much more accurate estimation on the actual demand than statistical data on demand which contains no explanation on the activity. However, usual generators in Japan are calibrated at different timing from the Master milkers: It is calibrated at 12:00 of third day in use. Only Sunday is counted as non-use day. Therefore, a generator used from Monday is calibrated on Wednesday and that from Saturday is calibrated on the next Tuesday.

In USA, the generators are usually calibrated on the day of manufacture and the highest activity one is 20 Ci.

ANSTO [1] has been supplying generators twice in a week for domestic use from Monday and from Thursday, respectively. Their activities are calibrated on the day of first use. Generators shipped on Friday are calibrated on Monday, and those shipped on Wednesday are calibrated on Thursday. Generator activities are usually less than or equal to about 3.25 Ci, but 10 Ci jumbo generators for radiopharmacies are also available. If the 10 Ci generator is calibrated on the day of manufacture, the generator loaded on Friday becomes 21.3 Ci and that on Wednesday becomes 12.9 Ci.

Based on above information, the scheme of ^{99}Mo supply in Australia is guessed as Figure A.3-1. They intentionally avoid works during weekend. If they work during weekend, decay time of generators used from Monday can be reduced by two days. The twice supplies per week are to reduce difference in available ^{99m}Tc between weekdays. From a viewpoint utilizing the ^{99}Mo in an optimum way, the second use of ^{99m}Tc generators from Wednesday is better than that from Thursday, but it may require target replacement on Sunday. They may be reluctant to work during weekend, and/or the work during weekend may not be so beneficial because it increases manpower cost.

A.3.3 Cost to use ^{99}Mo

Decay of ^{99}Mo inherently causes the higher cost to use it at the longer distances by its delivery time. Of course, there are several other factors affecting the cost depending on countries. Some typical cases are presented here.

(1) USA

USA is the largest ^{99}Mo consumer in the world, but they do not produce it by themselves. They usually imported ^{99}Mo solution from Canada and then distributed ^{99m}Tc generators.

The Committee on Medical Isotope Production Without Highly Enriched Uranium of US National Academies [1] (the Committee hereinafter) estimated the cost of ^{99}Mo in the USA at three different steps; production of ^{99}Mo solution, manufacturing ^{99m}Tc generators and administration of ^{99m}Tc to patients.

The cost to produce ^{99}Mo solution consists of costs for uranium target preparation, irradiation in the reactor and chemical processing. However, the Committee had confident that the irradiation cost does not include all of actual costs but, at best, covers only a share of reactor operational cost. From public sources of information about ^{99}Mo producers' revenues and the quantities of ^{99}Mo they supply, the Committee estimated a unit cost to produce ^{99}Mo solution US$225±100/six-day-Ci. As the demand of USA was about 6,000 six-day-Ci/w (300,000 six-day-Ci/y) in 2006, the overall cost to produce the ^{99}Mo solution to satisfy the US demand was about US$70M in a year.

The number of generators delivered in 2005 was 92,500 in USA. The Committee estimated that the "average" cost of a 10 Ci generator is about US$1,900±25%. Then the total sale of generators is US$176M/y, which is about 2.5 times of the cost for ^{99}Mo solution. The total activity of generators is 925,000 Ci. It is about three times of total ^{99}Mo solution activity expressed by the six-day-Ci, which corresponds to about 40 h decay after the shipment of ^{99}Mo solution. As the generators in USA are manufactured after one or two days from the shipment of ^{99}Mo solution and they are usually calibrated on the date of manufacture, it is reasonable.

Total number of ^{99m}Tc doses in USA was 24.3M in 2006. The average price per dose reported from a company in 2006 ranged from US$8.20 for hospital/clinic sales and US$7.2 for radiopharmacy sales. Most of ^{99m}Tc pertechnetate prices in 2008 fell in the range from US$0.28 to US$0.45 per mCi. The Committee assumed US$11.00/dose by taking the middle of the price range and assuming 30 mCi/dose. Then the total cost for the Tc-99m is US$267M/y, which is about 3.8 times of the cost for ^{99}Mo solution. Actual average dose is much less than the 30 mCi, but it may be compensated by the difference in timing determining the activity of ^{99m}Tc. If above prices of ^{99m}Tc pertechnetate per mCi is based on the activity when a company hands over to a hospital not when it is administered to the patient, then the 30 mCi/dose would be reasonable.

An average amount of ^{99}Mo used for a dose to a patient in USA can be estimated about 0.013 six-day-Ci/dose. It means that 1 six-day-Ci is used for about 80 doses in average. It is quite many doses compared to the price of ^{99}Mo solution but there would be some room to cover more doses. As aforementioned, in USA, the ^{99}Mo solution activity in six-day-Ci is similar with the activity at 12:00 Wednesday. As explained in the appended Section A.2.5, if the ^{99m}Tc is obtained at 09:00 every working day of a week by eluting 1 Ci generator calibrated at 12:00 Wednesday with 90% elution efficiency and then used for administration at 11:00, the total ^{99m}Tc available for administration during one working week is about 4 Ci. If the efficiency for the ^{99m}Tc generator loading is assumed 0.9, 3.6 Ci ^{99m}Tc is available from 1 six-day-Ci ^{99}Mo solution. Then the 0.013 six-day-Ci/dose of ^{99}Mo is equivalent to 47 mCi/dose of ^{99m}Tc. The Committee assumed 30 mCi/dose, but it is the maximum activity per dose in the usual practice. Actual dose to a patient is usually from a few to 20 mCi ^{99m}Tc. It indicates that the ^{99m}Tc used for the actual administration is a small portion or the average time to administration after elution is much longer than 2 h, i.e., a large portion of ^{99m}Tc is just decayed out without use. But hospitals might not have interest in the optimum use of ^{99}Mo because its price in the payment of patients is negligible.

The price of ^{99}Mo solution listed in the homepage of MDS Nordion on 7 December 2009 was US$1,500/six-day-Ci. They noted "*The price of the ^{99}Mo isotope produced by MDS Nordion represents only a minute fraction (less than 1 %) of the cost of a medical imaging diagnostic procedure*". As the Committee mentioned, the list price cannot be the actual price, however, it is too high compared to the estimation of Committee. It indicates that recently the price was increased significantly, especially due to the shortage of ^{99}Mo. The price near the end of 2009 would be two or three times of the best estimation by the Committee.

A statement [2] at the hearing on H.R. 3276, the American Medical Isotopes Production Act of 2009, included a phrase "*The shortage of this isotope, which usually costs only $10 of a multithousand dollar procedure, is threatening the healthcare of millions of Americans.*" It backs afore note of MDS Nordion.

(2) Australia

ANSTO supplies ^{99m}Tc generators for domestic users. Therefore, even though they produce the ^{99}Mo solution, they say only the price of generators. List price of a generator sold by ANSTO is composed of a fixed price and incremental price per ^{99}Mo activity. While majority of the incremental cost would be the price of ^{99}Mo solution and the fixed cost would be majority of additional cost to make the generators from the ^{99}Mo solution. When the incremental and fixed costs are estimated from generator prices in a figure shown in the reference [1], the fixed price is about A$560/generator. The incremental prices are about A$670 and A$430 per Ci for generators calibrated on Monday and Thursday, respectively (see Figure A.3-1). If the incremental prices are calculated for the activity on the day of shipment, they become around A$314 and A$336 per Ci, respectively. This indicates that the base of incremental price is the ^{99}Mo activity at shipping. If the price of 10 Ci generator is calculated so as to compare with the price in USA (US$1,900±25% for 10 Ci generator), it becomes about A$3,800. If the fact that actual price is lower than the list price, it seems that they are not significantly different.

R.E. Boyd [3] estimated the fixed and incremental costs of ANSTO, which were US$118/generator and US$57/six-day-Ci, respectively, which are too lower than above list prices to be explained by escalation and changes in exchange rate of currency. It may be due to the rather rapid escalation of ^{99}Mo price after his report.

(3) Japan

S. Kosuda [4] mentioned "*^{99m}Tc sale in Japan began in 1965 by importing generators from USA. From 1979, local companies have imported ^{99}Mo solution and distributed generators. Nowadays, Japan consumes 14% of world ^{99}Mo production second after USA (44%). One ^{99}Mo import by a company is about 10 TBq (270 Ci), and the company import 2 ~ 3 times in a week. The peak nuclear medicine market was ¥63B/y in 1995. In 2007, 1,219 nuclear medicine facilities performed 1,417,700 in vivo tests and 414,300 PET tests. In 2008, tests using ^{99m}Tc was about 50% of total tests. Disadvantages of ^{99m}Tc injection are high cost and difficulty for emergency use such as during night.*" As the world ^{99}Mo production is known 10,000 ~ 12,000 six-day-Ci/w, the 14% of world ^{99}Mo production corresponds to about 1,400 ~ 1,700 six-day-Ci/w. Since two companies imports ^{99}Mo 2 ~ 3 times each in a week, weekly import can be assumed 1,100 ~ 1,600 Ci or 1,350 Ci/w for a median. As these values are not so different from the 1,400 ~ 1,700 six-day-Ci/w, the 270 Ci for an import seems 270 six-day-Ci. If the statistics in 2008 was not so different from 2007, total number of tests using ^{99m}Tc in 2008 was about 920,000.

A radiopharmacy in Japan informed that a 500 Ci Master milker calibrated on Friday for its use from beginning of next week shares about 20% of ^{99}Mo in Japan, four Master milkers are made in a week, and about 20% remained is covered by usual generators. It means that about 2,500 Ci is used by the Master milkers and usual generators. In the previous study [5], ^{99}Mo demand in Japan was estimated 600 ~ 700 Ci/w when the activity of a generator is calibrated at the middle of a working week during the generator is in use, which is equivalent with the activity expressed by the six-day-Ci if ^{99}Mo solution suppliers are within short distance. It means that Japan imports more than twice of USA or Europe to make a same activity generator for the compensation of decay during delivery of ^{99}Mo solution.

The reference price for a usual ^{99}Mo/^{99m}Tc generator noticed by Japanese government on 1 April 2008 was ¥262 – 266 per 10 MBq which corresponds to about ¥970,000/Ci (about

US$10,000/Ci). Since the activity of each portable generator in Japan is calibrated at 12:00 on third day in use, five days decay time (generator manufacture on Friday and calibration on next Wednesday) is taken into account to compared with the US$1,900±25% for 10 Ci generator in USA. Then the price of 10 Ci generator is about US$28,000 in Japan, which is very high compared to any other data presented in this section.

Statistics on the distribution of radioisotopes in Japan in 2008 [6] show that 1.42E14 Bq of ^{99m}Tc generators were distributed, which correspond to 73.4 Ci/w for the total activity of generators in a week. It is much smaller than the 20% of 600 ~ 700 Ci/w. The reason would be that a portable generator can be ordered for the use from any working day except Sunday while the import of ^{99}Mo solution is twice or three times in a week, which means that additional decay time is inevitable for some generators of which supply timing does not match with the timing of ^{99}Mo solution import. If it is assumed that about 265,000 vials of labeling kits distributed in 2008 were used by hospitals using the 73.4 Ci/w of usual generators, an average ^{99}Mo activity per vial is 0.0144 Ci. A usual cold kit supplied from a company can be used for multiple doses, but it is not certain whether the vial in the statistics is for one or multiple doses. As the average ^{99}Mo activity per vial is similar with aforementioned average ^{99}Mo activity per dose in USA (0.013 six-day-Ci/dose), it is supposed that a vial is used for a dose. As the total sale of usual generators in 2008 was about ¥3.7B and if they are used for about 265,000 doses, the average cost of portable ^{99m}Tc generators per dose is about ¥14,000. The cost of ^{99}Mo for the administration should include additional cost in the hospital for the preparation of nuclear medicine. Then it must be higher than ¥14,000/dose.

The ^{99}Mo used for Master milkers produces ^{99m}Tc pertechnetate and labeled compounds for their sale to hospitals and clinics. The reference price for ^{99m}Tc pertechnetate was ¥275 ~ 279 per 10 MBq (some more than US$10,000/Ci). In 2008, 3.07E14 Bq of ^{99m}Tc (8,300 Ci/y = 160 Ci/w) were distributed for injections [6], of which total reference price is ¥8.45B when only the price of ^{99m}Tc pertechnetate is taken into account. When medians in the activity of labeled compounds per dose for respective categories (4 mCi/dose for heart, lung, liver, spleen and kidney applications, and 15 mCi/dose for brain and bone applications) are used, the total number of doses calculated becomes about 820,000 doses. Then, the average cost of ^{99}Mo from Master milkers is about ¥10,000/dose. It is less expensive than above mentioned ¥14,000/dose for the average generator cost per dose. However, S. Kosuda [4] mentioned that ^{99m}Tc injection is high cost compared to the use of generators. As the price of injection usually includes cost for labeling at the radiopharmacy, it may be higher than the ¥14,000/dose. It is not certain which makes the price of ^{99m}Tc injection high between the price of ^{99m}Tc pertechnetate from Master milker and the cost of labeling at the radiopharmacy.

From a general viewpoint, since the usage of a Master milker can be more effective than using many portable generators, it is understood that the average cost of ^{99}Mo per dose through Master milkers is lower than that through usual generators. However, that through Master milkers (¥10,000/dose) is still much higher than that in USA (US$11/dose).

Total number of doses in Japan in 2008 is a sum of doses using the usual generators (265,000) and the Master milkers (820,000), which is around 1.1M dose/y. It is a little larger than aforementioned 920,000 tests in 2008. In an interview with specialists in nuclear medicine on 12 November 2009 [7], the reporter said that about 1.42M *in vivo* inspections per year are carried out using nuclear medicine in Japan and more than 70% of them (more than 1M/y) are done using ^{99m}Tc, and a specialist commented more than 0.9M/y by ^{99m}Tc. Therefore, the total number of tests using ^{99m}Tc in Japan can be assumed about 1M per year.

If the 1M dose/y by 1,350 six-day-Ci/W in Japan is compared with the 24.3M dose/y by 6,000 six-day-Ci/w in USA, Japan consumes ^{99}Mo production more than 5 times of USA for a test. As the decay during import of the ^{99}Mo solution reduces the available activity below a half, additional decay to less than a half occurs after the solution arrived in Japan. It indicates that the pattern using ^{99}Mo in Japan is quite different from USA, and it is one of reasons that the cost of ^{99}Mo per dose in Japan is so expensive.

(4) Korea

Korea imports ^{99}Mo solution and portable ^{99m}Tc generators. Since all imported ^{99}Mo solution is used to manufacture portable ^{99m}Tc generators as well, all ^{99m}Tc in Korea for medical usage is obtained from portable generators. In the previous study [5], the ^{99}Mo demand of Korea was estimated about 100 Ci/w when the activity is calibrated at middle of a working week while the generators are in use.

Rather specific estimation of ^{99}Mo demand and price in 2007 is possible from two reports of Korea Radioisotope Association [8,9]. In 2007, total number of ^{99m}Tc generators distributed in Korea was 7,135 of which the total activity was 4,813 Ci, and 8,970 Ci ^{99}Mo was imported by ₩2.62B. The difference between total activities distributed by generators and of imported ^{99}Mo may come from different timing in calibration. The average unit price of imported ^{99}Mo is ₩292,000/Ci. As this price is just a little higher than the cost of ^{99}Mo in USA estimated by the Committee (US$225±100/six-day-Ci), the activity may be expressed by the six-day-Ci. The total activity of generators averaged over a week is 92.3 Ci/w. Therefore, it can be said that Korea imported 8,970 six-day-Ci to use 4,813 Ci because of decay during import. The decay of ^{99}Mo during its solution transportation is a little less than Japan, but not so different. Then the 92.3 Ci/w can be said as the ^{99}Mo demand of Korea in 2007. The fact that the total number of SPECT examination has been increased as shown in Figure A.3-2, confirms above mentioned 100 Ci/w for the current demand in Korea.

No data has been found how much hospitals paid for the generators. Total number of *in vivo* inspections in Korea using nuclear medicine except PET was 558,242 in 2007. If it is assumed that more than 70% of them were done using ^{99m}Tc as in Japan, about 390,000 doses of ^{99m}Tc in 2007 are expected. Then the cost of ^{99}Mo solution per dose is about ₩6,700. The average cost to use the ^{99}Mo for a dose should include additional unit costs to manufacture the generators and to prepare nuclear medicine for administration in the hospitals, but information to guess such additional cost is not found. The only value found is that the total income of hospitals from above 558,242 *in vivo* inspections was ₩104B, from which ₩186,000/inspection is derived as an average value.

The average activity of ^{99}Mo per dose is about 0.0123 Ci of generator activity, which is similar with 0.013 six-day-Ci/dose in USA and 0.0144 Ci/dose for usual generators in Japan. It indicates that the efficiency utilizing ^{99m}Tc generators except Master milkers is similar in the three countries.

The frequency of SPECT examination in Korea is still increasing as shown in Figure A.3-2. If it is taken into account that the decrease during 1998 ~ 2000 was due to sudden price increase of imported generators, overall trend over past 20 years was almost steady increase. However, the recent increase of PET is very fast, which indicates that many inspections to be done by ^{99m}Tc are being replaced by the PET. In 2009, the frequency of PET was more than a half of SPECT. Meanwhile current frequency of SPECT by ^{99m}Tc per unit population is similar with Japan – some less than 1 %/person-year, which is some less than 20% of USA. As the frequency of inspections using ^{99m}Tc in Japan was already saturated and gradually decreasing, the frequency in Korea would not increase so much in the future.

(5) Vietnam

Vietnam imports ^{99m}Tc generators. D.V. Dong [10] introduced market prices of ^{99m}Tc generators in Vietnam in 2006. From his data, the fixed and incremental prices are estimated about US$820 and US$1,900/Ci, respectively. There is no mention on the calibration timing of the generators. Since the activities of generators presented are only 0.2, 0.3 and 0.4 Ci, and as such low activity generators calibrated on the first day of use would be difficult to use, their calibration timing would be the same as in Japan and Korea. The high fixed price would be due to air transportation of the generators from a long distance and the high incremental price would be due to long decay time.

Since their domestic demand is small, installation and operation of a ^{99m}Tc generator loading facility would be difficult to be justified yet. As the imported ^{99m}Tc generators are very expensive, they have much stronger motive to use the (n,γ)^{99}Mo than other countries above mentioned.

(6) Analysis of European Nuclear Society

In the cost analysis of ^{99}Mo/^{99m}Tc generators by the European Nuclear Society (ENS) [11], the price for a thyroid scan with ^{99m}Tc on an adult outpatient in a Belgian university hospital was exampled. In the total cost €130, the price of isotope was €19.

From a small survey (8 data in total were received from Europe, North and South America, and Oceania), following data are presented:

- ^{99m}Tc generator price

  €3.7 ~ €24 /GBq, average €12 /GBq (€137 ~ €888 /Ci, average €444 /Ci)

  Without extremes:

  €6.7 ~ €18.2 /GBq, average €11.5 /GBq (€248 ~ €673 /Ci, average €426 /Ci)
- ^{99m}Tc dose price

  €2 ~ €19 /GBq, average €7.4 /GBq (€2.2 ~ €21 /30mCi, average €8.2 /30mCi)

  Without extremes:

  €2.4 ~ €9.5 /GBq, average €5.8 /GBq (€2.7 ~ €10.5 /30mCi, average €6.4 /30mCi)

When above prices of generator is compared with US$1,900±25% for the 10 Ci generator in USA, only the lowest extreme (€137/Ci) is close to the US price. It indicates that the timing for activity calibration would be different in addition to differences in the size of generators, transport cost, market conditions, etc. When above ^{99m}Tc dose prices are compared with US$11 per 30 mCi dose in USA, the average price is not so different from the USA price. Differences in medical systems and cost between countries may be the major reason showing the wide range of ^{99m}Tc dose price surveyed. The exampled price for a thyroid scan €130 is not so different from the average price of an *in vivo* inspection in Korea ₩186,000.

The ENS also cited statements of reliable sources: "*The price for irradiation is market price, which does most probably not cover the marginal cost, and certainly does not take the investment and decommissioning costs into account. The irradiation is heavily subsidized. The irradiation price is roughly estimated to be between 5 and 10% of the cost of the generator. The price of the separation phase seems to be barely above the true cost. The benefit margin is said to be less than 5%*"

The position paper by CEA, NRG, SCK•CEN and TUM on 13 April 2010 stated "*The world value of nuclear medicine imaging agents associated with* ^{99m}*Tc is estimated by the medical industry as being of the order of €1,000M or more per year.* ^{99}*Mo radiochemical market value can be estimated at 15-20 % of the* ^{99m}*Tc nuclear medicine imaging agents market value. The reactor irradiation services market value can be estimated at 10-15 % of* ^{99}*Mo radiochemical market value. Therefore it can be calculated that the* ^{99}*Mo irradiation services market value is presently only 1.5% to 3% of the nuclear medicine imaging agents market value. The supply has been essentially subsidized by existing governmental infrastructure investment. It is foreseen that irradiation costs must increase substantially in order to pay for the security of supply required by Medicine today.*"

A.3.4 Concluding remarks

The ^{99}Mo activity expressed by six-day-Ci represents a demand of ^{99}Mo to fission Mo solution suppliers. In USA and Europe where respective suppliers and users are within short distance, the activity by six-day-Ci is close to the actual demand. For Japan and Korea who need a longer time interval between production and usage of the ^{99}Mo, however, the ^{99}Mo activity available to users is much less than the activity by six-day-Ci. It makes the unit cost of ^{99}Mo solution higher than USA and Europe, which is estimated about twice of USA. Therefore, the low cost for local (n,γ)^{99}Mo production can make it more competitive than in USA.

Compared to the fission Mo, the (n,γ)^{99}Mo costs much less for production but is less convenient and costs more for use. However, since the cost portion of fission Mo in the payment of a patient is already sufficiently small in many countries which consume rather large amount of ^{99}Mo, reducing the cost for the production of ^{99}Mo does not give meaningful influence to the end users. Instead, if it gives any disadvantage in the imaging process which causes additional cost to compensate it, the (n,γ)^{99}Mo is hardly possible to compete with the fission Mo. While the impact to the usage in the hospitals should be sufficiently small, the room to accommodate the impact to the manufacturing of ^{99m}Tc generators is relatively large. The cost portion of ^{99}Mo in the price of a ^{99m}Tc generator is the larger for the higher activity generator. Therefore, the room to the jumbo generators should be much larger than the portable generators.

Since all generators in Korea have been portable generators, in order to replace them by the (n,γ)^{99}Mo generators, the additional cost to make them must be reasonable. It will be especially important for the lower activity generators. Therefore, increasing the specific activity of (n,γ)^{99}Mo is important to minimize the size of generator.

In Japan, only four 500 Ci Master milkers share about 80%. Therefore, relatively high investment to replace the Master milker by a new device using the (n,γ)^{99}Mo and some higher cost for its operation may be accepted. If a device extracting high concentration ^{99m}Tc from the low specific activity ^{99}Mo is available, the high specific activity of ^{99}Mo would not be so critical requirement as the case of portable generators. However, as the cost portion of ^{99}Mo solution in the price of isotope for dose is much lower than other countries, the impact from irradiation cost including cost for targets may be relatively small as well. Flexibility in the supply of ^{99}Mo during a week such as twice or three times supply per week may also be needed.

As actual cost for the target irradiation is not fully reflected in the current price of ^{99}Mo solution but subsidized by the public of the country operating the reactor, and the post processing of the fission Mo remains a large amount of radwaste in the country operating the chemical facility, there is a concern how the production of ^{99}Mo for its usage at other countries can be justified. The ^{99}Mo consumption of USA is about a half of global usage, but they do not produce any ^{99}Mo. Therefore, countries supplying ^{99}Mo to USA may argue that their people pay tax for the reactors and take risk from the facilities and radwaste but a large portion of the ^{99}Mo is used for the health of USA people. The USA has been giving a lot of effort to replace the HEU targets to LEU, but it remains more radwaste in the countries supplying the ^{99}Mo to USA, which can be hardly accepted by the supplying countries. The USA is now implementing the American Medical Isotopes Production Act which provides fund to the development of non-HEU technologies for sufficient and reliable production of ^{99}Mo in USA by the end of 2013. NNSA (National Nuclear Security Administration) expects the elimination of HEU export for ^{99}Mo production in 7 to 13 years [13]. Reactor operators of Europe also emphasized the regional production of ^{99}Mo for its long term stable availability.

The price of future ^{99}Mo will cover full cost for its production including capital cost of reactor and decommissioning. If Japan and Korea continue the import of ^{99}Mo from long distances, they will pay twice of the escalated price but its availability will not be as robust as the region producing the ^{99}Mo. Japan consumes the ^{99}Mo more than twice of any other countries for an inspection. The high ^{99}Mo consumption per inspection in Japan would be understood that Japanese isotope companies have given higher priority to the convenience rather than to the efficiency in its usage. They may also have utilized the low efficiency as a buffer against shortage in supply, i.e., they have a large room to increase the efficiency when the supply is reduced. However, it is questionable whether their excuse can be accepted by patients paying much more for the ^{99}Mo than other countries and the people of countries supplying the ^{99}Mo with burden of radwaste.

References

[1] Medical Isotope Production Without Highly Enriched Uranium, Nuclear and Radiation Studies Board, Division of Earth and Life Studies, NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, THE NATIONAL ACADEMIES PRESS, Washington D.C. www.nap.edu, 2009.

[2] https://www.hsdl.org/?view&doc=120491&coll=public, Hearing on H.R. 3276, the American Medical Isotopes Production Act of 2009, December 3, 2009.

[3] R.E. Boyd, The gel generator: a viable alternative source of ^{99m}Tc for nuclear medicine, *Appl. Radiat. Isot.* Vol. 48, No. 8. pp.1027-1033, 1997.

[4] S. Kosuda, Importance of a ^{99}Mo/^{99m}Tc generator and a perspective of nuclear medicine in the face of difficult situation of supply shortage of ^{99m}Tc from the viewpoint of a nuclear medicine specialist, RADIOISOTOPES, 59, pp.329-339 (2010). In Japanese.

[5] B.J. Jun, et al, Revaluation of ^{99}Mo production by (n,γ) method at HANARO, JAEA- Review 2010-032, July 2010.

[6] Statistics on the distribution of radioisotopes and disposal of radioactive waste in Japan, Japan Radioisotope Association, 2008. In Japanese.

[7] http://www.innervision.co.jp/12SP/voice/interview/vol005/index.html, read on 12 May 2010. In Japanese.

[8] Statistics on the radiation practices in Korea, Korea Radioisotope Association, 2009.7. In Korean.

[9] Investigation on the status of radiation and radioisotope utilization in Korea, Nov. 2008,

Korea Radioisotope Association, MEST. In Korean.

[10] Edited by E.Z. Sombrito and T. Genka, Development of PZC-based Tc-99m Generator – Issue-2, FNCA, March 2007.

[11] High Scientific Council – Position Paper, The medical isotope crisis, e-news issue 26, Autumn 2009, http://www.euronuclear.org/e-news/e-news-26/hsc-statement.htm.

[12] Position paper by CEA, NRG, SCK・CEN & TUM, Scenario for sustainable molybdenum-99 production in Europe, 13 April 2010, http://www.nea.fr/med-radio/docs/Multisources%20Mo-99%20production%20scenario%20for%20Europe%20%20Position%20paper-CEA-NRG-TUM-SCK%20CEN.pdf

[13] P. Staples, Molybdenum-99 production without the use of HEU – New developments and next steps, Meeting IAEA CRP Feasibility Evaluation of the Use of LEU Fueled Homogenized Aqueous Solution Nuclear Reactors for the Production of Short Lived Fission Product Isotopes, 22 Feb. 2010.

[14] Korean Society of Nuclear Medicine, http://www.ksnm.or.kr/, visited on May 2010.

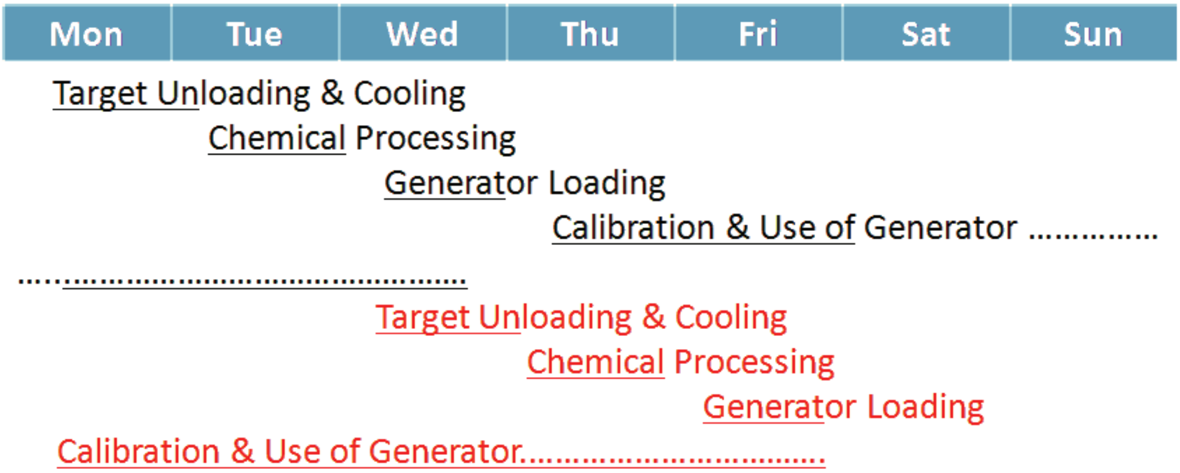


Figure A.3-1. Guessed scheme of ^{99}Mo supply in Australia

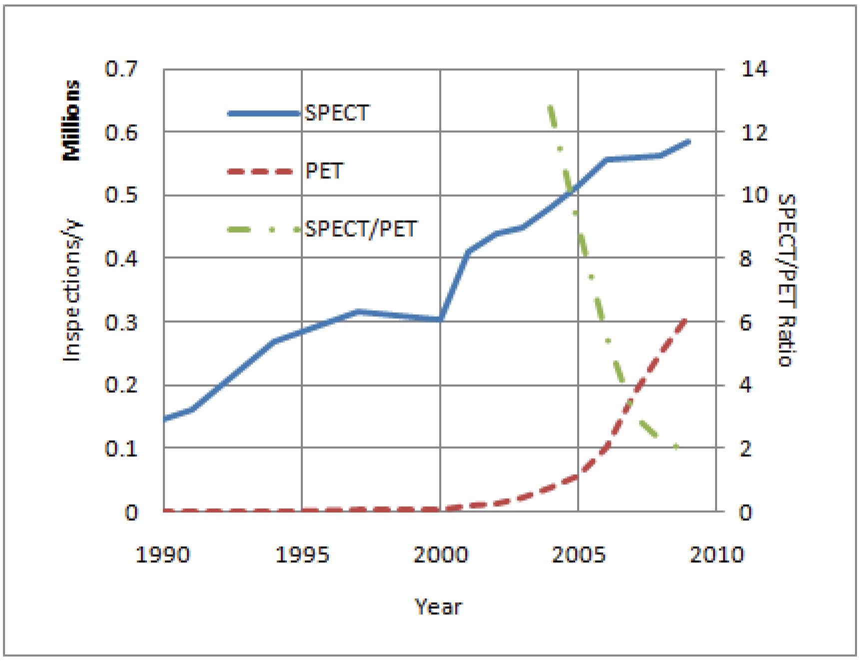


Figure A.3-2. Trend of SPECT and PET inspection frequencies in Korea [14]

A.4 Extraction of ^{99m}Tc

A.4.1 Introduction

The (n,γ)^{99}Mo encounters only one high hurdle - how to make its users to extract the ^{99m}Tc in a convenient and cost effective way. Of course, the ^{99m}Tc extraction from the fission Mo using ^{99m}Tc generators is a reference of comparison. Since the specific activity of (n,γ)^{99}Mo is extremely lower than the fission Mo, much more amount of Mo is involved in the ^{99m}Tc extraction and the simple process used for the fission Mo becomes difficult to apply. Therefore, its convenience cannot be equivalent to nor better than that from fission Mo, but the advantage of (n,γ)^{99}Mo in all other aspects may compensate the deficiency in the extraction of the ^{99m}Tc.

In the scheme using the fission Mo, each generator company makes many generators. If the inconvenience in the process for the use of (n,γ)^{99}Mo is limited to the companies producing generators and does not propagate to the users of generators, some complex process in the production of generators may be accepted. It is especially important to portable generators which are used at hospitals. For a radiopharmacy using jumbo generators or Master milkers for the supply of ^{99m}Tc nuclear medicines to many hospitals, if the inconvenience is only to the radiopharmacy and does not propagate to the hospitals, some complex process in the ^{99m}Tc extraction may be accepted.

As explained in appended Section A.3, the cost for the fission Mo solution used in Japan and Korea has been at least about twice of USA due to the long distance delivery. Therefore, the (n,γ)^{99}Mo produced by local reactors in Japan and Korea is much more competitive than USA. In addition, the activity of a Master milker in Japan is about 25 times of the highest activity among jumbo generators used in USA. The Master milker is actually equipment installed in a hot cell rather than a generator frequently replaced. A company operating the Master milker loads it as well, which may give additional room to accommodate the (n,γ)^{99}Mo.

Here, ^{99m}Tc extraction methods from (n,γ)^{99}Mo are reviewed from a viewpoint to figure out the feasibility of mass (n,γ)^{99}Mo supply. There had been other methods reported such as thermal separation methods, but they are not included here because they have not been actually used. The ^{99m}Tc extraction from fission Mo is also described in Section A.4.2 as the reference of comparison. It is assumed that the ^{99m}Tc extracted from the (n,γ)^{99}Mo has at least equivalent performance in its use, as that from fission Mo. If there is any problem in its use, the problem must be duly investigated and resolved in advance.

A.4.2 Extraction from fission Mo

Extraction of ^{99m}Tc from the fission Mo is accomplished by elution of a ^{99m}Tc generator containing an alumina column. The Mo adsorption capacity of alumina is said typically 2 mg-Mo/g-alumina [1] or limited to 20 mg-Mo/g-alumina [2,3]. We suppose that the 20 mg-Mo/g-alumina is a maximum capability and the 2 mg-Mo/g-alumina is a practice with sufficient margin to prevent Mo breakthrough for actual uses. Therefore, the amount of alumina needed for a generator column is estimated based on the 2 mg-Mo/g-alumina.

From ^{235}U fission, Mo isotopes of mass number 95, 97, 98, 99, 100 are produced with similar yield each other. Among them the ^{95}Mo in the recovered Mo is very small because half lives of its precursors ^{95}Zr and ^{95}Nb are 64 and 35 days, respectively. While other Mo isotopes are stable, ^{99}Mo decays during irradiation. Therefore, isotopic ratio of ^{99}Mo decreases with irradiation time. After the end of irradiation, as the ^{99}Mo decays out, its isotopic ratio decreases almost exponentially. If we assume that the production ratio of ^{99}Mo in the total Mo is 1/4 and that the irradiation time is 7 days, the isotopic ratio of ^{99}Mo in the total Mo is around 13.5 % at the end of irradiation. If the decay time until generator loading is also assumed as 7 days for conservatism, it reduces to 2.6 % at the generator loading.

Then, for a 500 Ci Master milker calibrated at the time of milker loading, the amount of ^{99}Mo is about 1 mg and total Mo is about 40 mg when the milker is loaded. Therefore, 20 g alumina is sufficient for the column of a Master milker. For the highest activity jumbo generator in USA, which is 20 Ci at the time of generator loading, 0.8 g alumina is sufficient. For a 5 Ci portable generator, 0.2 g alumina is sufficient. Therefore, the size of column is almost negligible in the volume of shielded container.

The generator loading process is simple. Predetermined amount of ^{99}Mo solution is added to each alumina column; the columns are washed and then packed into shielded containers for shipping. A ^{99m}Tc generator loading facility can make hundreds of generators in a day. The process extracting the ^{99m}Tc from a generator is only one elution using saline solution. The elution from a usual generator needs only a few minutes. Elution of a Master milker may require more time, but much less than an hour. Actual difference may come from handling of eluate due to the higher activity. Japanese radiopharmacies operating Master milkers load the milkers by themselves.

Since the ^{99}Mo activity per unit volume of alumina column is high, high concentration ^{99m}Tc eluate is obtained as well.

When we compare processes extracting the ^{99m}Tc from the (n,γ)^{99}Mo with above processes, three different cases may be considered; 1) for use of portable generators at hospitals, 2) for use of jumbo generators by radiopharmacies, and 3) for use of Master milkers by radiopharmacies. However, we focus cases 1) and 3), because case 2) is neither found in Japan nor in Korea. We can imagine that the case 2) would be in between them. When we use (n,γ)^{99}Mo, supplying ^{99m}Tc instead of ^{99}Mo may also be possible, but it cannot be accepted from majority of current fission Mo users.

For the case 1), a generator loading company makes many generators for many hospitals, and, once a generator is made, it is usually used at the hospital for a week. Therefore, integration of a small inconvenience in the extraction of ^{99m}Tc at the hospitals becomes a large impact. Therefore, the inconvenience to the hospitals from the use of (n,γ)^{99}Mo must be minimized and confined to the generator company as much as possible. However, it is challenging to the company as well, because the inconveniency in the manufacturing of a generator may also be multiplied by the number of generators they produce.

For the case 3), the inconvenience must be limited to the radiopharmacies loading and operating the Master milkers. Since each company deals with a large amount of ^{99}Mo, a benefit using the low cost (n,γ)^{99}Mo is also large. Their final products are ^{99m}Tc nuclear medicines not ^{99m}Tc generators. Therefore, a completely different process from the use of Master milker may also be considered, if available.

A.4.3 Extraction from (n,γ)^{99}Mo

A.4.3.1 Solvent extraction

In general, solvent extraction method employs methyl ethyl ketone (MEK) to extract ^{99m}Tc from ^{99}Mo. After dissolution of MoO_3 powder in a NaOH solution, the solution is mixed well with MEK, and then the MEK containing the ^{99m}Tc is separated. Substantial steps are required to re-extract the ^{99m}Tc from the MEK and purify it as a radiopharmaceutical. This process is called as liquid-liquid extraction or MEK method as well. It was used from the beginning of ^{99m}Tc era and is still used for small local supplies of ^{99m}Tc at several research reactor centers. Its process became simplified and convenient to use [1], but must be much more difficult to be used in a hospital than the use of ^{99m}Tc generator. It can deal with a large amount of MoO_3 but actual amount of ^{99m}Tc supply has been limited due to short half-life of ^{99m}Tc.

For the mass (n,γ)^{99}Mo supply, this method may be used by radiopharmacies, especially by the Master milker operators in Japan. Once the device is installed, it is used repeatedly. The fact that such devices have been used at several research reactor centers for small scale local supplies of ^{99m}Tc indicates that its capital cost will share little in the routine large amount extraction. Cost for chemicals and waste must be sufficiently small compared to the fission Mo extraction from irradiated uranium targets. Time needed to extract the ^{99m}Tc by the solvent extraction was 30 minutes by J.D. Lee [4]. A little longer time may be needed for the large scale extraction, which is longer than the elution time of a Master milker. Therefore, majority of deficiency compared to the use of the Master milker may come from the time needed for the ^{99m}Tc extraction. But its impact to cost would be sufficiently less than the benefit from the use of low cost (n,γ)^{99}Mo compared to the use of imported fission Mo solution.

However, there has been no experience of a large scale ^{99m}Tc extraction by this method. When an irradiation hole just outside of HANARO core is used for the target irradiation [5], the amount of natural MoO_3 for the extraction of ^{99m}Tc equivalent to the Master milker is about 400

g. If enriched ^{98}Mo is used, about 100 g is needed. A less amount of target material is expected when a highest neutron flux hole available for the ^{99}Mo production at JMTR is used, due to not only the higher neutron flux but also the shorter target transportation time to the companies.

In a personal communication, J.S. Lee who operates the solvent extraction device in KAERI, mentioned that the solvent extraction method is not so limited by the amount of MoO_3 and the current device in KAERI dissolves 130 g MoO_3 in 600 mL NaOH, of which activity is more than 10 Ci. He expected no difficulty to dissolve the 400 g MoO_3. He supposed that following items should be checked for the large scale ^{99m}Tc extraction; ^{99m}Tc extraction efficiency, residual Mo, ^{99}Mo, MEK, by-products from radiolysis of MEK such as methanol and ethanol, and labeling efficiency of HMPAO. HMPAO shows lowest labeling efficiency among ^{99m}Tc labeled compounds by ^{99m}Tc eluate from fission Mo, because it is easily ionized. Affect from inactive Mo and ^{99m}Tc compounds with MEK, etc. should be checked. His group has a plan to test above items at higher activity than before.

For the routine mass extraction, there would be some room to optimize the device by increasing automation to reduce manpower cost. Anyway, experimental confirmation of the method is necessary for the application to routine mass extraction.

A.4.3.2 Zr gel generator

The Zr gel generators loaded with $(n,\gamma)^{99}$Mo adsorbed in zirconium molybdate gel (ZMG) have been used at hospitals of some countries. P. Saraswathy et al [2] introduces history of ZMG generator technology especially its technology transfer through IAEA technical cooperation activities, as well as Indian history in the supply of ^{99m}Tc. In India, only Bhabha Atomic Research Center (BARC) has been producing and supplying the $(n,\gamma)^{99}$Mo. They have intended to keep a certain domestic capability for the stable availability of ^{99}Mo by the $(n,\gamma)^{99}$Mo. For many hospitals in India, delivery of ^{99m}Tc from BARC takes too long time compared to its half-life. Therefore, the solvent extraction devices have been used at the user ends as well. As discussed in the previous section, however, it is inconvenient for use at a hospital. Therefore, for a long time, Indian researchers have made effort to replace the solvent extraction devices at hospitals by the ZMG generators. The ZMG process is very complex and requires elaborate remote handling. However, once the complex work is done at the BARC, the gel generators are delivered to distant hospitals for their convenient uses. Loading 50 g Mo to ZMG granules takes about 4.5 h by the optimized process that they developed.

R.E. Boyd [6] explains properties of ZMG which causes the complex process. He tested the ZMG for portable and jumbo generators, and compared their cost with generators using the fission Mo based upon actual Australian production yields and cost. As the ^{99m}Tc solution obtained from $(n,\gamma)^{99}$Mo/^{99m}Tc jumbo gel generators is too dilute for immediate clinical application, he used a convenient ^{99m}Tc concentration step as well. As the gel generator is also eluted by solute-free water, he used 1 g alumina column to adsorb ^{99m}Tc from the eluate of the generator and then eluted the alumina column with small amount of saline solution to get high concentration ^{99m}Tc. As the title of his paper indicates, the gel generator technology could be a viable alternative source of ^{99m}Tc for nuclear medicine. However, since his paper was published in 1997, ANSTO has never used the technology for actual supply of ^{99m}Tc generators.

As the cost portion of ^{99}Mo solution in a portable generator is relatively small, the complex process to make the ZMG generator would cost more in Australia than the cost saving from the use of $(n,\gamma)^{99}$Mo. For a jumbo generator, as the cost portion of ^{99}Mo solution is large, the cost saving from the use of $(n,\gamma)^{99}$Mo may sufficiently compensate the additional cost to make the jumbo gel generator at the generator loading step. However, at the next step, the bulky jumbo gel generator causes inconvenience and additional cost for use, which may not be accepted by radiopharmacies in Australia. Meanwhile, in addition to the complex process of the gel generator, K. Tatenuma [1] assumed inferior reproducibility of ^{99m}Tc elution rate, a higher breakthrough of ^{99}Mo, etc.

Anyway, in many countries, it seems that the ZMG generator technology is difficult to be adopted.

A.4.3.3 Other potential methods

There are two emerging high Mo adsorbents reported as potential materials for the ^{99m}Tc generator application. They are PZC (poly-zirconium compound) and ALSUL (alumina functionalized with sulfate).

The PZC [1,7] was originally synthesized by JAERI (Japan Atomic Energy Research Institute) and Kaken Co. Ltd. in Japan. The characteristics of generators using PZC and $(n,\gamma)^{99}$Mo were proven in terms of eluate quality, bio-distribution tests using mice showed very satisfactory result, clinical trials were successfully carried out, and its commercial approaches were already studied. All FNCA (Forum for Nuclear Cooperation in Asia) member states except Australia participated in the test of PZC.

The process to make PZC generators is much simple compared to ZMG generators, and a semi-automated pilot machine loading up to 8 generators simultaneously was developed and tested. An optimum condition of Mo adsorption is 3 h at 90 °C, and total operation time of the machine from ^{99}Mo loading into the machine to column packing of PZC loaded with the ^{99}Mo has been shorten to 4 ~ 5 h. A large scale production machine dealing with up to 100 units was conceptually designed. The production time of this machine was assumed to be approximately 6 ~ 8 h.

Therefore, the PZC is ready for actual uses and has sufficient justification to replace the ZMC generators. It also has potential to replace some portable generators but not adopted for actual use yet. L. Yishu [7] introduced gel generator of NPIC (Nuclear Power Institute of China) including difficulties and problems but concluded "*Because good technology and facilities exist in CIAE and NPIC for the routine production of the generator, there is little possibility for setting up a new facility for the routine production of PZC ^{99m}Tc generator*".

The ALSUL [8] is a synthetic alumina functionalized with a sulfate moiety, developed by KAERI. Its capability for ^{188}W/^{188}Re generator application was proven by a series of test, and test for application to ^{99}Mo/^{99m}Tc generators using (n,γ)^{99}Mo is under way. The actual maximum capacity of W adsorption is about 80 % of theoretical value, which is about 500 mg-W/g-ALSUL. As the PZC also has 500 mg-W/g-PZC adsorption capacity [1], the adsorption capacity of Mo is expected almost the same as PZC. The exchange reaction rate between the tungstate and the sulfate moiety on the pore surface of the adsorbent is fast enough to load the tungstate into the column already filled in ALSUL, which allows the same process of fission Mo loading into alumina column. Therefore, it is expected that the process and time for the (n,γ)^{99}Mo loading into the ALSUL column will not be so different from the fission Mo loading into alumina column. It has a high potential to improve the ^{99m}Tc generator technology using the (n,γ)^{99}Mo significantly, but its short history will require a certain time for the full verification.

For a portable generator, if high neutron flux and enriched ^{98}Mo targets are used, the volume of (n,γ)^{99}Mo based PZC or ALSUL column is still small enough. For a jumbo generator, however, the column volume must be much larger than the fission Mo based alumina column. The larger column volume causes a larger shielding of the column and a lower ^{99m}Tc concentration in the eluate. The cost increment coming from the larger shielding must be sufficiently compensated by the low cost for the (n,γ)^{99}Mo solution. If the radiopharmacy requires higher ^{99m}Tc concentration than that achievable by the (n,γ)^{99}Mo based generators, an additional step increasing the ^{99m}Tc concentration in the eluate is needed.

An important difference in the elution of the PZC and ALSUL columns, compared to the ZMG column, is that they are not easily eluted by the solute-free water. Therefore, the simple ^{99m}Tc concentration step used by R.E. Boyd [6] cannot be applied to the PZC and ALSUL generators. It is the same case for the conventional alumina column when it is used for the ^{188}W/^{188}Re generator or (n,γ)^{99}Mo based ^{99m}Tc generator. J.S. Lee et al [8] mentioned that available approach to solve the low ^{188}Re concentration problem was the use of a concentration method. T.H. Bokhari et al [9] reviewed various methods of concentration and suggested a new one. S. Chattopadhyay and M.K. Das [3] also reported a technique for the effective concentration of ^{99m}Tc and stated that the technique may be equally applicable for the effective concentration of $^{188}ReO_4^-$ from ^{188}W/^{188}Re generators.

Therefore, the PZC or ALSUL jumbo generator combined with a ^{99m}Tc concentration kit may open a possibility to satisfy the radiopharmacies who require the high concentration ^{99m}Tc. They may compare this option with the solvent extraction method which is explained in Section A.4.3.1, and choose a preferred one. We cannot exclude other better options which would be emerged in the near future, too.

A.4.4 Concluding remarks

There have been many efforts to overcome the extremely low specific activity of $(n,\gamma)^{99}$Mo, and potential methods expected to improve the convenience and cost effectiveness greatly in the use of $(n,\gamma)^{99}$Mo are under test. They cannot be equivalent to nor better than the use of fission Mo, but the advantage of $(n,\gamma)^{99}$Mo in all other aspects may allow some deficiency in the extraction of ^{99m}Tc. As the cost for the fission Mo imported in Japan and Korea is at least about twice of USA, Japan and Korea have a larger room to accept the use of $(n,\gamma)^{99}$Mo.

The PZC is almost ready for actual uses and has sufficient justification to replace the Zr gel generators. It also has potential to replace some fission Mo based portable generators. However, its long loading time would cause a limitation for the mass supply of portable generators.

The ALSUL is promising for the mass supply of portable generators, but its short history will require a certain time for the full verification. To satisfy hospitals using the $(n,\gamma)^{99}$Mo based ALSUL generators, the specific activity of ^{99}Mo must be as high as possible, which can be achieved by irradiating enriched ^{98}Mo targets in the high neutron flux.

The large difference in the costs between the $(n,\gamma)^{99}$Mo produced by local reactors and the imported fission Mo may give both PZC and ALSUL a potential to replace the Master milkers in spite of much large column size and additional burden to concentrate the ^{99m}Tc. Of course, verification of the ^{99m}Tc concentration technology especially for the impact to the labeling processes will be needed. Meanwhile, the conventional solvent extraction method can also be an option to replace the Master milkers. The technology is already proven, but its application to high activity may require verification. We cannot exclude other better options which would be emerged in the near future, too.

References

[1] Edited by T. Genka, Development of PZC-based Tc-99m Generator – Issue 1, FNCA, March 2006.

[2] P. Saraswathy, et al., Tc-99m generators for clinical use based on zirconium molybdate gel and (n,γ) produced Mo- 99: Indian experience in the development and deployment of indigenous technology and processing facilities, 2007 International RERTR Meeting, www.rertr.anl.gov, read on 13 April 2010.

[3] S. Chattopadhyay and M.K. Das, A novel technique for the effective concentration of ^{99m}Tc from a large alumina column loaded with low specific-activity (n,γ)-produced ^{99}Mo, Applied Radiation and Isotopes, 66 (2008), pp.1259-1299.

[4] J.D. Lee and B.H. Lee, A convenient method on the methyl-ethyl-ketone extraction of $^{99m}TcO_4^-$, *J.* Korea Radiation Protection Society, v9, No.2, pp.103-111, 1984.

[5] B.J. Jun, et al, Revaluation of ^{99}Mo production by (n,γ) method at HANARO, JAEA- Review

2010-032, July 2010.

[6] R.E. Boyd, The gel generator: a viable alternative source of ^{99m}Tc for nuclear medicine, *Appl. Radiat. Isot.* Vol. 48, No. 8. pp. 1027-1033, 1997, Elsevier Science Ltd., Printed in Great Britain

[7] Edited by E.Z. Sombrito and T. Genka, Development of PZC-based Tc-99m Generator – Issue-2, FNCA, March 2007.

[8] J.S. Lee, et al., Development of a high performance ^{188}W/^{188}Re generator by using a synthetic alumina, Applied Radiation and Isotopes, 67 (2009) pp.1162-1166.

[9] T.H. Hussain, et al., Lead cation exchange and alumina columns for concentration of 99mTc-pertechenate, *J. Radioanalytical and Nucl. Chem.*, v 279, No 1 (2009) pp.281-285.

A.5 Review of Szilard-Chalmers enrichment for the (n,γ)^{99}Mo production

A.5.1 Introduction

International Union of Pure and Applied Chemistry (IUPAC) [1] defines the Szilard–Chalmers effect "*The rupture of the chemical bond between an atom and the molecule of which the atom is part, as a result of a nuclear reaction of that atom.*" The Szilard–Chalmers enrichment is a technology utilizing the Szilard–Chalmers effect for selective extraction of the atoms produced by the nuclear reactions. A symposium report of the American Chemical Society in 1957 [2] introduced that the rupture of carbon-iodide bond by neutron activation of iodine in ethyl iodide was discovered in 1934 by Szilard and Chalmers and then the phenomenon had been utilized for the preparation of samples of very high specific activity where such would be difficult or impossible to obtain by other methods. In 1961, however, G.E. Boyd et al [3] concluded "*the advantage of the Szilard-Chalmers effect should disappear as progressively more intense slow neutron sources become available*" based on a series of experiments for the Szilard-Chalmers enrichment of ^{82}Br using K_2BrO_3 at a low neutron flux facility. As high neutron flux research reactors became available, the Szilard-Chalmers enrichment has been no more utilized for routine radioisotope production.

Rather recently, however, preliminary experiments to increase the specific activity of medical radioisotopes produced by (n,γ) method were reported by D. Jansen [4] of NECSA in South Africa for ^{117m}Sn, and then by B.S. Tomar et al [5] of Delft University in Netherland for ^{90}Y and ^{99}Mo. The World Nuclear News [6] informed that B. Wolterbeek of Delft University applied a patent for a new ^{98}Mo(n,γ) method using neutrons from other than reactors. Details were not disclosed but the news indicated that it is one method of Szilard–Chalmers enrichment.

This report reviews the Szilard–Chalmers enrichment to check whether its application to the mass production of (n,γ)^{99}Mo will be feasible.

A.5.2 Review of previous works

In 1947, W.F. Libby [7] summarized observed Szilard-Chalmers phenomena in the early time when only weak neutron sources were available: When least hydrolysable liquid organic halide was irradiated by thermal neutrons and then product halide was extracted by water, a certain portion of the activated halide was obtained. The recovery was 30 ~ 70%, which was specific to each compound. Dilution of the target substances by solvent increased the recovery, but very low concentration was needed for meaningful reduction of the loss from the retention (= 1 - recovery). Vaporization of the target substance reduced the retention to very few percents. Addition of aniline ($C_6H_5NH_2$) to bromobenzene (C_6H_5Br) in small percentages greatly decreased the retention. This summary indicates that the enrichment was possible with the cost for significant loss of production capability.

In the same year, R.R. Williams [8] reported the effect of intense radiation field of the chain-reacting pile to the Szilard-Chalmers enrichment for various antimony compounds and potassium ferrocyanide. His experiment indicated that the successful Szilard-Chalmers enrichment achieved at low neutron fluence and low background gamma rays did not ensure its success at high neutron fluence and high background gamma rays.

In 1961, G.E. Boyd et al [3] reported irradiation effect to the Szilard-Chalmers enrichment of ^{82}Br by neutron irradiation of potassium bromate (K_2BrO_3). The neutron irradiation time was from 0.25 to 64 h at 6.7x10^{11} n/cm^{2}-s of thermal neutron flux in Oak Ridge pile. Irradiated K_2BrO_3 powder was dissolved in the water and then carbon tetrachloride (CCl_4) was used to extract Br separated from BrO_3^{-}. They found that the product of neutron fluence and enrichment factor was almost constant but slowly decreasing with the neutron fluence, i.e., the enrichment factor decreases a little more rapidly than the increase of neutron fluence. At the highest thermal neutron fluence of 1.54x10^{17} n/cm^{2} achieved by the experiment, the enrichment factor was 47. If the trend continues at the higher neutron fluence, there will be no enrichment when the fluence is 47 times of 1.54 x10^{17} n/cm^{2}, which is equivalent to 20 h irradiation at 1x10^{14} n/cm^{2}-s thermal neutron flux. The recovery decreased a little as the neutron fluence increased. Based on these results, they foresaw that the advantage of Szilard-Chalmers effect from the irradiation of K_2BrO_3 should disappear at strong neutron source.

In the same year, H. Ebihara and K. Yoshihara [9] reported hot atom effects of some metal oxinates (8-hydroxyquinoline, C_9H_7NO). They dissolved irradiated dehydrated oxinates of Mo (15 h at 4.8x10^{11} n/cm^{2}-s), In (10 min. at 6x10^{11} n/cm^{2}-s) and W (15 h at 2.8x10^{11} n/cm^{2}-s) at JRR-1, in an organic solvent, and then extracted activation products. They got 0.5 ~ 2 % activity with enrichment factor of 10 ~ 130 for the Mo, nearly 100 % activity with enrichment factor of 10^{6} for the In, and about 34 % activity with enrichment factor of 430 for the W.

In 2005, D. Jansen [4] reported test results to get enriched ^{117m}Sn by irradiating SnO and SnO_2 at low flux positions in SAFARI-I for 1, 7 or 8 days. Any data to guess the neutron fluence were not given, but the fluence would be much higher than aforementioned cases. The test for the production of high specific activity ^{117m}Sn was unsuccessful and a case that was mentioned 'some promising result' seems quite doubtful.

In 2006, K.P. Zhernosekov [10] reported the Szilard-Chalmers enrichment for ^{166}Ho production by irradiating Ho-DOTA at 4x10^{12} n/cm^{2}-s neutron flux of TRIGA II Mainz in Germany. The neutron flux was one order higher than those of previous tests in early 1960s. It shows that Szilard-Chalmers enrichment for Ho-DOTA was working at this neutron flux. He also presented more promising results reported for the enrichment of ^{166}Ho by Shapkin et al at 5x10^{13} n/cm^{2}-s neutron flux of VVR-M in 1977. However, as analyzed in the next section, the 'promising results' are quite doubtful.

In 2008, B.S. Tomar et al [5] reported irradiation results for yttrium oxinate and yttrium oxide nano powder having particle size about 20 nm. Each irradiation was for about 10 minutes at 5 x10^{12} n/cm^{2}-s neutron flux of 2 MW Delft University reactor. They also irradiated molybdenum oxinate and molybdenum hexacarbonyl complexes for 1 – 4 h at the same neutron flux. Best enrichment factors of ^{90}Y were 8 with 19% yield for the Y-oxinate and 7 with 1.2% yield for the Y-oxide. For the case of ^{99}Mo, enrichment factor 66 with 10% yield for the Mo-oxinate and 18 with 20% yield for the Mo-hexacarbonyl were reported.

In the same year, the World Nuclear News [6] informed that B. Wolterbeek applied a patent for a new ^{98}Mo(n,γ) method using neutrons from other than reactors. It was described “the energy transfer involved separates the water-soluble ^{99}Mo from the surrounding atoms”. Details were not disclosed.

There must have been much more works on the Szilard-Chalmers enrichment. However, we suppose that the review of above works is enough to judge the usefulness of the Szilard-Chalmers enrichment for the mass (n,γ)^{99}Mo production.

A.5.3 Theoretical modeling and comparison with experiments

Among the works reviewed in the previous section, reports of G.E. Boyd et al [3] and K.P. Zhernosekov [10] presented rather specific data to compare with theoretical model. They already compared their data with their models. Their model neglected backward flow from separable to non-separable states such as recombination. Neglecting the backward flow did not cause any significant problem because the backward flow was very small due to the low concentration at the separable state. However, the backward flow becomes significant at high neutron fluence. In this section, a model including the backward flow is derived and the Szilard-Chalmers enrichment at high neutron fluence is examined using the model.

The flow of target and product atoms during neutron irradiation is conceptually drawn in Figure A.5-1. An atom of interest can be at one of four states by combination of two phases - non-separable/separable and target/product. For the case of K_2BrO_3 target used by G.E. Boyd et al for the production of ^{82}Br, ^{79}Br (50.69% abundance) and ^{81}Br (49.31% abundance) compose the raw target atoms. During neutron irradiation, ^{80}Br and ^{82}Br are produced by neutron capture of ^{79}Br and ^{80}Br, respectively. Among them, only ^{82}Br is the product and ^{80}Br remains as the target. Any Br isotope bounded in the K_2BrO_3 or any other chemical form from which the Br cannot be separated by the post process is non-separable, otherwise separable. Therefore, the non-separable chemical form is not limited to the K_2BrO_3. Though the original chemical form is broken and another molecule is made but the Br atom in the new molecule is not separated by the post process, it is non-separable. Balance equations for target and product atoms at respective chemical states are derived based on Figure A.5-1.

Balance equations for the target and product atoms regardless of chemical state are Eq.s (1) and (2), respectively.

$$\frac{dN}{dt} = -\phi\bar{\sigma}N \tag{1}$$

$$\frac{dN^*}{dt} = -\lambda N^* + \phi\sigma a N \tag{2}$$

with initial conditions of $N(0) = N_0$ (1-0)

and $N^*(0) = 0$, (2-0)

where N and N^* are total numbers of target and product atoms, respectively, φ is neutron flux, $\bar{\sigma}$ is microscopic depletion cross section of target, λ is decay constant of product nuclide, σ is microscopic neutron capture cross section for the production reaction, and a is abundance of the target isotope giving the product.

When the $\phi\bar{\sigma}$ is very small, the loss of target nuclides by burnup in Eq. (1) can be neglected. Above two experiments to be analyzed and the irradiation of Mo for ^{99}Mo production fall in this case. Therefore, the total number of target atoms N can be assumed as a constant, and the balance equation for the total product atoms becomes a simple form as Eq. (2-1).

$$N = N_0 = \text{constant} \tag{1-1}$$

$$\frac{dN^*}{dt} = -\lambda N^* + pN_0\,, \tag{2-1}$$

of which solution is

$$\frac{N^*(t)}{N_0} = \frac{p}{\lambda}(1 - e^{-\lambda t}) \tag{2-2}$$

where, $p = \phi\sigma a$. (3)

As the irradiation is going on, both of target and product atoms can exist at either separable or non-separable state.

$$N = N_n + N_s = N_0 \tag{4}$$

$$N^* = N_n^* + N_s^* \tag{5}$$

where subscript-n, subscript-s, no superscript and superscript-* at N denote non-separable, separable, target and product states, respectively.

In the balance equation for the target atoms at separable state, the burnup loss term can also be neglected as approximated in Eq. (6).

$$\frac{dN_s}{dt} = -(p + k)N_s + KN_n \cong -kN_s + KN_n = -(K + k)N_s + KN_0 \tag{6}$$

with initial condition $N_S(0) = 0$ (6-0)

where, K = probability that an atom at the non-separable state transits to separable state per unit time by radiochemical rupture of chemical bond, and

k = probability that an atom at the separable state transits to non-separable state per unit time by recombination.

Its solution is Eq. (6-1).

$$\frac{N_S(t)}{N_0} = \frac{K}{\beta}(1 - e^{-\beta t}) \tag{6-1}$$

where, $\beta = K + k$. (7)

The solution for $N_n(t)$ can be obtained by Eq.s (4) and (6-1), if it is needed.

The balance equation for the product atoms at separable state is Eq. (8), and its solution becomes Eq. (8-1).

$$\frac{dN_s^*}{dt} = -(\lambda + k)N_s^* + rpN_s + (1 - R)pN_n + KN_n^* \tag{8}$$

$$\frac{N_s^*(t)}{N_0} = A(1 - e^{-\alpha t}) + B(1 - e^{-\lambda t})e^{-\beta t} + C(1 - e^{-\beta t})e^{-\lambda t} \tag{8-1}$$

where, R = probability that a product atom captured a neutron at the non-separable state is retained at the same state (retention factor), and

r = probability that a product atom captured a neutron at the separable state remains at the same state (remaining factor),

$$\alpha = \lambda + K + k , \tag{9}$$

$$A = [\frac{rK + (1 - R)k}{\beta} + \frac{K}{\lambda}]\frac{p}{\alpha} , \tag{10}$$

$$B = \frac{(1 - R - r)Kp}{\beta\lambda} , \tag{11}$$

and $$C = -\frac{Kp}{\beta\lambda} . \tag{12}$$

The solution for the $N_n^*(t)$ can be obtained from Eq.s (2-2), (5) and (9-1), if it is needed.

G.E. Boyd et al [3] measured decomposition (D), recovery (φ), specific activity (S), enrichment factor (ε) versus neutron fluence for the production of ^{81}Br(n,γ)^{82}Br by neutron irradiation of K_2BrO_3. We can estimate some parameters in above equations from their data to compare our model with their measurement.

The decomposition D is the portion of total Br atoms at the separable state expressed by Eq. (13), and its trend when t is sufficiently small can be approximated as Eq. (13-0).

$$D(t)=\frac{N_s(t)+N_s^*(t)}{N_0} \tag{13}$$

$$D_{t\to 0}=\{K+[\frac{rK+(1-R)k}{\beta}+\frac{K}{\lambda}]p\}t\cong Kt \tag{13-0}$$

Therefore, the *K* can be estimated from measured *D/t* values for sufficiently small *t.* The trends of measured *D* and *D/t* are compared with calculations in Figure A.5-2. The sudden jump of *D/t* at 5th point (1.33 h of irradiation time) may be due to actual sudden increase of the decomposition or due to difference in sample preparation. While the average value for all measured *D/t* is 9.0x10^{-5} /h, it is 9.7x10^{-5} /h when the four data of short time irradiation up to 1 h are excluded. G.E. Boyd et al got 97 ppm/h by fitting the *D* versus *t* for data longer than 1 h irradiation only. For the prediction of long term irradiation effect here, the 9.7x10^{-5} /h is chosen for the *K*. A sensitivity study showed that the next influential parameter determining the *D* in Eq. (13) is *k*, and influences of others are negligible. As shown in Figure A.5-2, calculation and measurement agrees very well when *k* is 0. When the *k* is significantly larger than the *K* (40 times in the figure), the deviation becomes the larger for the longer irradiation time. Therefore, it seems that the *k* is not so large compared to *K*. However, *k* = 40 *K* gives a good agreement between calculation and measurement for the recovery φ, which will be explained soon.

Figure A.5-3 shows the trend of decomposition versus source intensity (power of the neutron source) for a fixed 2 h irradiation. The decomposition is almost proportional to the source intensity. It is quite reasonable because the decomposition is proportional to the radiation level at the irradiation target, which is proportional to the source intensity. Therefore, the *K* can be set as Eq. (14).

$$K=\chi\phi \tag{14}$$

where χ is a constant specific for each irradiation condition. When the χ is calculated by the *K* estimated above and the neutron fluxφ of 6.7x10^{11} n/cm^2-s, it becomes 4.03x10^{-20} cm^2 (40,300 b). Its unit is the same as the microscopic cross section.

The recovery φ is the portion of ^{82}Br at the separable state among total ^{82}Br produced. It is expressed by Eq. (15) with its initial and saturated values by Eq.s (15-0) and (15-1).

$$\varphi(t)=\frac{N_s^*(t)}{N^*(t)} \tag{15}$$

$$\varphi_{t\to 0}=1-R \tag{15-0}$$

$$\varphi_{\infty}=\frac{A\lambda}{p} \tag{15-1}$$

Since the values of recovery measured for 2 h fixed irradiations were around 0.73 regardless of source intensity, the retention factor R is estimated as 0.27 from Eq. (15-0). However, the recovery shows a decreasing trend with irradiation time as in Figure A.5-4. A sensitivity study for Eq. (15) showed that the decreasing trend is governed by the k. To make the trend of calculated φ values by Eq. (15) agrees with that of measured ones as in the figure, the k should be 40 times of K. When the k is small, the recovery should be almost independent of irradiation time in this neutron fluence range but measured trend is gradually decreasing. In the previous analysis, however, the calculated decomposition versus irradiation time agreed well with measurement when the k was neglected. It indicates a possibility that the K may not be a constant but may increase with irradiation time.

For the case of specific activity, as its unit rd./mg used by G.E. Boyd et al is not understood, values of relative specific activity S are calculated by Eq. (16) to compare their trend with that of measured ones. Its initial and saturated values are Eq.s (16-0) and (16-1).

$$S(t) = \frac{N_S^*(t)}{N_S^*(t) + N_S(t)} \tag{16}$$

$$S_{t \to 0} = \frac{p(1-R)}{K} = \frac{\sigma a(1-R)}{\chi} \tag{16-0}$$

$$S_\infty = \frac{A\beta}{K} \tag{16-1}$$

As compared in Figure A.5-5, the trend of calculated specific activity is similar with that of measured. The specific activity is insensitive to the k as shown in the figure.

The enrichment factor ε is the ratio of specific activity achieved by the separation to that of overall. As the overall relative specific activity S_o corresponding to Eq. (16) is Eq. (17), the enrichment factor becomes Eq. (18) with initial and saturated values of Eq.s (18-0) and (18-1).

$$S_o(t) = \frac{N^*(t)}{N_0} \tag{17}$$

$$\varepsilon(t) = \frac{S(t)}{S_0(t)} \tag{18}$$

$$\varepsilon_{t \to 0} = \frac{1-R}{Kt} + R + r \cong \frac{1-R}{Kt} \tag{18-0}$$

$$\varepsilon_\infty = \frac{KA}{p\beta} \tag{18-1}$$

Figure A.5-6 compares the enrichment factors calculated by Eq. (18) with measured ones. The variation shape of calculated values with irradiation time is similar with the measured one, but differences in the absolute values are rather large. It is the same case when the enrichments versus source strength for 2 h irradiations are compared. Since the product of enrichment factor ε and t is almost a constant close to $(1 - R)/K$ for small t from Eq. (18-0), the εt

is good to judge the difference between calculation and measurement. As shown in Figure A.5-7, calculated εt values using R and K previously estimated for the decomposition D and the recovery φ are larger than twice of measured ones. The εt is insensitive to k as shown in the figure and a sensitivity study showed that it is not sensitive to the r too. Therefore, the mismatch in the figure should come from uncertainty in R and K, but the reason of mismatch is not found. Since the recovery φ is the ratio of activities between separated and total products, its measurement was rather easy compared to the measurement of decomposition D, for which determination of very small amount of separated atoms is involved. The neutron activation analyses for the samples sufficiently decayed out would give reliable D values, but the technology might not be available at that time. Therefore, we can give more credit to the measured recovery than the decomposition, which means the R fits to the measured recovery φ is more reliable than the K fits to the measured decomposition D. When the R fits to the measured recovery φ is used, the K fitting to the measured enrichment factor ε is more than twice of that previously estimated. However, we will use the K previously estimated, because we can consistently say that our prediction on enrichment will give higher values than actual ones.

The terminology ‘enrichment factor’ may mislead the effectiveness of the Szilard-Chalmers enrichment. Our ultimate goal is to increasing the specific activity, which can be basically achieved by sufficiently long irradiation at as high neutron flux as possible. When the Szilard-Chalmers enrichment is not applied, the maximum specific activity achievable is the saturated specific activity. Therefore, the ratio of S to saturated S_o is the proper parameter to evaluate the effectiveness of the Szilard-Chalmers enrichment. From Eq. (17) the saturated S_o becomes Eq. (17-1), and then the effectiveness of the Szilard-Chalmers enrichment E becomes Eq. (19) with initial and saturated values of Eq.s (19-0) and (19-1).

$$S_{o,\infty} = \frac{p}{\lambda} \tag{17-1}$$

$$E(t) = \frac{S(t)}{S_{0,\infty}} = \frac{\lambda S(t)}{p} \tag{19}$$

$$E_{t \to 0} = \frac{\lambda(1-R)}{K} \tag{19-0}$$

$$E_{\infty} = \frac{A\beta\lambda}{Kp} \tag{19-1}$$

Figure A.5-8 compares measured and calculated values of effective enrichment E. Its trend is the same as that of specific activity shown in Figure A.5-5 except difference in magnitude. Here also, the calculated values are more than twice of measured ones. In this experiment, the effective enrichment achieved was more than 20. Since it is inversely proportional to p as shown in Eq. (19), however, it will become smaller as the neutron flux increases. The neutron flux in the above study was 6.7x10^{11} n/cm^2-s, which is very low for the meaningful (n,γ)^{99}Mo production.

K.P. Zhernosekov [10] tested the Szilard-Chalmers enrichment for Ho-DOTA at TRIGA II Mainz reactor. Enrichment factors and retention values for irradiations at neutron flux 4x10^{12} n/cm^2-s were presented. The estimated K, χ and R from presented data are as 0.0157, 1.09x10^6 b and 0.1546, respectively. Figures A.5-9 and A.5-10 compares calculated enrichment factor and recovery with measured ones. In these calculations, other unknown factors are assumed as r = 1 and k = 3.89x10^{-3} which are same values used for the analysis of aforementioned experiment on K_2BrO_3. Sensitivity study showed that the enrichment factor and recovery are not sensitive to r in the range of fluence used for the experiment. When the other extreme value 0 is assumed for the r, the recovery shows gradually decreasing trend with irradiation time. While the enrichment factor is not sensitive to the k, the recovery gradually decreases when k is large. However, while the k is smaller than 6 times of 3.89x10^{-3} (neutron flux of this experiment is about 6 times of previous one), the calculated recovery (φ) values are almost the same as those in Figure A.5-10.

When the Ho-DOTA is compared with K_2BrO_3, the retention factor R is reduced from 0.27 to 0.1546, but the χ is increased 27 times from 4.03x10^4 b to 1.09x10^6 b, and the k for the K_2BrO_3 can also be used for the Ho-DOTA. It seems that K_2BrO_3 is better compound for the Szilard-Chalmers enrichment than the Ho-DOTA, but the fact that gamma levels per neutron flux at the irradiation positions for the two experiments might be different should also be taken into account.

K.P. Zhernosekov introduced a result of Shapkin et al for irradiation of sulfurated diphtalocyanin complex of ^{165}Ho at VVR-M reactor as a case given more promising results. The neutron flux was 5x10^{13} n/cm^2-s, which was about one order higher than his experiment. However, reported enrichment factors versus irradiation time show very different trend from calculation as shown in Figure A.5-11. Therefore, the data are very doubtful.

For the competitive (n,γ)^{99}Mo production nowadays, the neutron flux should be at least 200 times of that G.E. Boyd et al used, i.e., 1.34 x10^{14} n/cm^2-s. We estimate the recovery φ and the effective enrichment ε for the irradiation of K_2BrO_3 at such high neutron flux.

We assume that the decomposition factor K will become 200 times from Eq. (14). For the case of the recombination factor k, it is not certain whether it will become 200 times as well or remain as a constant. If the migration volume of the decomposed atom is large enough, then the k will be proportional to the number density of radicals produced by the decomposition. However, atoms in the solid target do not migrate so much and the decomposed atom and radical are located very near each other. Therefore, the recombination would usually occur between them. If the decomposition is significant, however, the probability of recombination with other radicals will increase and the k will become larger. Therefore, we can assume that the k will be in the range from a constant value which is 40 times of K at 6.7x10^{11} n/cm^2-s neutron flux to 200 times of this constant value. Actually none of K, k, R and r can be a constant because the irradiation at high neutron flux will change the chemistry and chemical environment significantly. But calculations assuming them constants may give us an insight whether the Szilard-Chalmers enrichment will be feasible or not at high neutron flux.

Figures A.5-12 and A.5-13 predict the recovery and the effective enrichment at high neutron flux and compare with those measured at low neutron flux. In order to get the most promising results by the calculation, it is assumed that every production reaction at separable state keeps the product at the separable state ($r = 1$). However, the figures clearly show that the Szilard-Chalmers enrichment no more exists for the irradiation of K_2BrO_3 at high neutron flux. In addition, if the k is proportional to the neutron flux, recovery will be very poor. It reconfirms the prediction of G.E. Boyd et al [3] – *the advantage of the Szilard-Chalmers effect should disappear as progressively more intense slow neutron sources become available*, unless the radiochemical characteristics of the target material are much superior than those of K_2BrO_3.

From Eq.s (19), (19-0) and (19-1), we can estimate a prerequisite condition that the effective enrichment E can be larger than 1. Figure A.5-14 depicts the trend of E versus irradiation time when $k = R = 0$ and $r = 1$, i.e., no recombination, no retention in the non-separable state by neutron capture at the non-separable state and no transition to the non-separable state by neutron capture at the separable state. In this case, $K = \lambda$ is the condition to make $E = 1$. For the non-zero retention factor R, it becomes $K = \lambda(1 - R)$ from Eq. (19-0).

Decomposition cross section χ for the $(n,\gamma)^{99}$Mo production is 2.92x10^4 b to make the effective enrichment 1 when $k = R = 0$, $r = 1$ and φ = 1x10^{14} n/cm^2-s. Since the K is proportional to the neutron flux which will be a few times of 1x10^{14} n/cm^2-s and other factors will not be ideal values as above, actual χ for $E = 1$ must be much smaller than 2.92x10^4 b. If it is compared with the χ of K_2BrO_3 which is 4.03x10^4 b, we can imagine that the χ of Mo target should be at least one order of magnitude lower value of the K_2BrO_3, i.e., less than 4000 b, so as to achieve meaningful Szilard-Chalmers enrichment for the $(n,\gamma)^{99}$Mo production. Therefore, first of all, a good compound having sufficiently small K with good characteristics for other parameters – small k and R but large r close to 1, should be found.

The decomposition cross section χ of the Ho-DOTA (1.09x10^6 b) is much larger than that of K_2BrO_3 (4.03x10^4 b). The much larger molecular size of DOTA ($C_{16}H_{24}N_4O_8$) than the K_2BrO_3 may be the reason. These decomposition cross sections are much larger than the neutron capture cross section of respective molecules, as well. Actually, virtually all decompositions occur due to ionizations by gamma rays not by neutrons. In the reactor, the gamma flux is similar order of neutron flux and average gamma ray energy is around 1 MeV. As the first ionization energy is in the range from a few to a few tens of eV, around 10^5 ionizations are expected per unit neutron flux. It may conceptually explain why above decomposition cross sections are so large. For the $(n,\gamma)^{99}$Mo production, epithermal neutron flux is effective and the gamma flux at the irradiation hole with high epithermal neutron flux is also high, which will make the χ larger. Then it is quite questionable whether a Mo compound having the χ value around 10^3 b or less will be available.

If the recoil of ^{99}Mo compound nucleus after neutron capture is very energetic and the decomposition due to the recoil can be distinguished from the ionization by gamma rays, there would be some way of selective extraction of the ^{99}Mo. The recoil energy is analyzed in the next section.

A.5.4 Recoil energy

When the atom produced by the nuclear reaction becomes sufficiently energetic to rupture its chemical bond, it is popularly called as 'hot atom'. If the chemical states of the hot atoms are different from the original one and are maintained until an appropriate chemical process to separate them, selective extraction of the produced atoms can be achieved. When the hot atom keeps the same atomic number but different mass number, i.e., an isotope, the selective extraction gives highly enriched isotope. If the isotope is radioactive, a high specific activity radioisotope is produced.

Since the specific activity of a radioisotope produced by the (n,γ) reaction is very low especially when the neutron capture cross section or the neutron flux is low, the Szilard–Chalmers enrichment was applied usually for the enrichment of (n,γ) reaction products. Actually Szilard and Chalmers discovered the phenomenon in the case of the (n,γ) process as well. Here, our concern is the low specific activity of (n,γ)^{99}Mo, therefore, we focus our discussion on the possible enrichment of (n,γ)^{99}Mo product.

In the (n,γ) reaction, if the kinetic energy of incident neutron E_n is sufficiently higher than the thermal vibration energy of the atom, about E_n/A is transferred to the kinetic energy of the compound nucleus and remaining $E_n(A - 1)/A$ is converted to its internal energy, where the A is the mass number of the product atom. For the case of a thermal neutron capture (around 25 meV of E_n in average), the energy transfer is negligible and the compound nucleus emits the first prompt gamma ray within about 10^{-16} s [11]. When the neutron capture state coincides with a quasi-stationary level of the compound nucleus, the neutron capture cross section has a peak, which is called resonance capture. In this case, since the E_n is usually in keV range, some kinetic energy is transferred to the compound nucleus and the life time of compound nucleus until its first prompt gamma ray emission is typically two or three orders of magnitude longer than the off-resonance nuclear status, i.e., 10^{-13} ~10^{-14} s. If the compound nucleus emits multiple gamma rays in a cascade, the nucleus reaches its ground status within 10^{-9} ~ 10^{-12} s due to a little longer transition time at the semi-stable energy state(s). When the half-life at a transition energy level is longer than 1 μs, it is called isomeric transition and else prompt gamma emission.

The recoil momentum from the emission of a photon with energy E_p is E_p/c. If the momentum of the compound nucleus at the timing of the photon emission cannot be neglected, its final momentum will become a vector sum with the recoil momentum from the photon emission. When it is a thermal neutron capture, the momentum of the compound nucleus can be neglected, and the recoil energy of the compound nucleus from the emission of a photon is $5.36\text{x}10^{-4}\ E_p^2/A$ when the MeV is used for the unit of energy.

For the case of ^{99}Mo compound nucleus produced by the capture of a thermal neutron, its mass equivalent energy over ground state of ^{99}Mo is 5.9265 MeV [12]. The compound nucleus decays to the ground state by emitting one or multiple prompt gamma ray(s) in a cascade. The maximum recoil energy is $5.36\text{x}10^{-4}$ x $5.9265^2/99$ MeV ≈ 190 eV when the compound nucleus emits one 5.9265 MeV prompt gamma ray. When multiple prompt gamma rays are emitted in cascade, the time interval between two consecutive gamma ray emissions is $10^{-9} \sim 10^{-12}$ s as aforementioned. G. Harbottle and N. Sutin [13] calculated that the time required to slow down a recoil atom of energy 300 eV and mass number 100 is about $1.3\text{x}10^{-13}$ s. Therefore, when the next prompt gamma ray is emitted, the recoil atom is already sufficiently slow and then the atom recoils again by the second prompt gamma emission. The lowest energy of the first prompt gamma ray from the ^{99}Mo is 3.3332 MeV when it transits to the next energy level at 2.5942 MeV. In this case the recoil energy from the first gamma is 60 eV, and the maximum recoil energy from the second gamma is 35 eV. Since the chemical binding energy of an atom in the stable molecules is from a few to a few tens of eV, it is expected that the chemical bond holding the ^{99}Mo atom is always ruptured by the recoil from prompt gamma emission. The energy range of ultraviolet light is 3 ~ 124 eV. Therefore, the 60 ~ 190 eV recoil energy of ^{99}Mo is equivalent to the photon energy of hard ultraviolet light and soft X-ray.

As shown in Figure 6 of main text, since the ^{98}Mo(n,γ) cross section decreases rapidly in the MeV energy range, fast neutrons are not so helpful for the production of ^{99}Mo. Majority of non-thermal neutron capture of ^{98}Mo are resonance reactions from about 10 eV to less than 100 keV. The recoil energy of ^{99}Mo compound nucleus from the capture of 99 keV neutron, for an example, is 1 keV and remaining 98 keV is transferred to the internal energy. Since the increment of ^{99}Mo compound nucleus internal energy is less than 2 % of 5926.5 keV, its impact to the prompt gamma recoil energy is almost negligible. The time required to slow down the hot atom of 1 keV kinetic energy is similar with the that for the first prompt gamma emission. Therefore, epithermal neutron capture can produce hotter atoms than the thermal neutrons capture, but majority of them is less than 1 keV.

W.F. Libby [7] set A keV, which corresponds to 99 keV for the ^{99}Mo, as a reasonable upper limit to the energy range in which ionization is improbable. G. Harbottle and N. Sutin [13] stated that, when a neutral atom of mass M has a kinetic energy E, if the portion of the kinetic energy shared by an electron ($m_e E/M$, where m_e is electron mass) is near its binding energy ε_b, there will be a finite probability for electron loss. Then the kinetic energy of a ^{99}Mo atom required for its ionization is about $1.8\text{x}10^5\ \varepsilon_b$. Since the first ionization energy of Mo is 7.1 eV, the kinetic energy of ^{99}Mo atom should be about 1.28 MeV for the first ionization. Therefore, the recoil ^{99}Mo atom will neither lose its electrons nor ionize the surrounding atoms.

Therefore, it can be said that the recoil energy of every ^{99}Mo atom produced by a neutron capture is sufficient to rupture the chemical bond of Mo, but too small for any ionization. During the cooling down of the hot atom, it may replace the location of non-active ^{98}Mo atoms by collisions, may make a new molecular form, or may become a free atom. The new location of the ^{99}Mo atom after settle down can be a few atoms apart from its original location. The free atom has possibility to recombine with a radical as time goes on. However, it would be difficult to distinguish from the ionized Mo atoms by gamma rays.

A.5.5 Concluding remarks

The Szilard-Chalmers enrichment works for neutron irradiation of only low fluence. In 1961, G.E. Boyd et al [3] predicted that the advantage of the Szilard-Chalmers effect should disappear at high neutron flux. However, rather recent reports on this subject are still found. It should also be pointed out that the neutron fluence used for the recent works are still very low. One promising result obtained in 1977 at $5x10^{13}$ n/cm^2-s neutron flux with maximum irradiation time 26 h shows quite different trend from that theoretically predicted, which makes the reliability of data quite doubtful.

The simulation reconfirms the prediction of G.E. Boyd et al, and indicates that an excellent material should be found to keep the advantage of Szilard-Chalmers effect at high neutron fluence. An important requirement to the material is the sufficiently low decomposition cross section, which is dominated by ionization process of gamma rays. For the $(n,\gamma)^{99}$Mo production, it should be less than 10% of K_2BrO_3 which was tested by G.E. Boyd et al. Since majority of gamma rays react with electrons, it is quite questionable whether a Mo compound having such low decomposition characteristics by gamma rays can be found.

If the recoil energy of the compound nucleus produced by neutron capture of ^{98}Mo is sufficiently high to distinguish the recoil atom from other atoms ionized by gamma rays, there would be some way to extract the product selectively. The maximum recoil energy from thermal and resonance neutron captures of ^{98}Mo are 190 eV and around 1 keV, respectively. The recoil energy is sufficient to rupture the chemical bond of Mo but too small for any ionization. The recoil atom would remain very near the original place and would easily recombine.

Therefore, it will be extremely difficult, if possible, to utilize the Szilard-Chalmers enrichment for the mass production of the $(n,\gamma)^{99}$Mo.

References

[1] IUPAC Compendium of Chemical Terminology 2nd Edition (1997), http://www.iupac.org/

goldbook/S06239.pdf

[2] R.H. Schuler, Introduction to the symposium on chemical effects of nuclear transformations, *J. Phys. Chem,* 1958, 62 (11), pp.1343-1344.

[3] G.E. Boyd, et al., Recoil reactions with high intensity slow neutron sources. I. The Szilard-Chalmers enrichment of 35.9 h Br^{82}, *J. Phys. Chem,* 1961, 65 (9), pp.1542-1546.

[4] D. Jansen, Developing a method for the production of high specific activity 117m Sn from tin oxides using the Szilard-Chalmer effect, 5th *Intl. Conf. Isotopes*, Brussels, Belgium, April 2005.

[5] B.S. Tomar, et al., Increasing the specific activity of medically useful radionuclides through Szilard Chalmers reaction, *Trans. Am. Nucl. Soc.* 2008, pp.880-881.

[6] http://www.world-nuclear-news.org/, New technique promises non-U medical isotopes, 16 September 2008.

[7] W.F. Libby, Chemistry of energetic atoms produced by nuclear reactions, *J. Am. Chem,* 1947, 69 (10), pp.2523-2534.

[8] R.R. Williams, The Szilard-Chalmers reaction in the chain-reacting pile, *J. Phys. Chem,* 1948, 52 (3), pp.603-611.

[9] H. Ebihara and K. Yoshihara, Preparation of molybdenum-99, indium-116m and tungsten-185 in a high specific activity, Bunseki Kagaku, 10, 48 (1961), main text in Japanese.

[10] K.P. Zhernosekov, Radiochemical aspects of production and processing of radiometals for preparation of metalloradiopharmaceuticals, Johannes Gutenberg- Universität Mainz, 2006. http://deposit.ddb.de/cgi-bin/dokserv

[11] G.L. Molnar, Handbook of prompt gamma activation analysis with neutron beams, Kluwer Academic Publishers, 2004.

[12] IAEA Coordinated Research Project for Development of a Database for Prompt Gamma-Ray Neutron Activation Analysis, http://www-nds.iaea.org/pgaa/PGAA database/reports/Mo/99mo_adopt.ens, visited on 18 June 2010.

[13] G. Harbottle and N. Sutin, The Szilard-Chalmers reaction in solid. Part I. Chemical effects of nuclear recoil, *J. Phys. Chem,* 1958, 62 (11), pp.1344-1351.

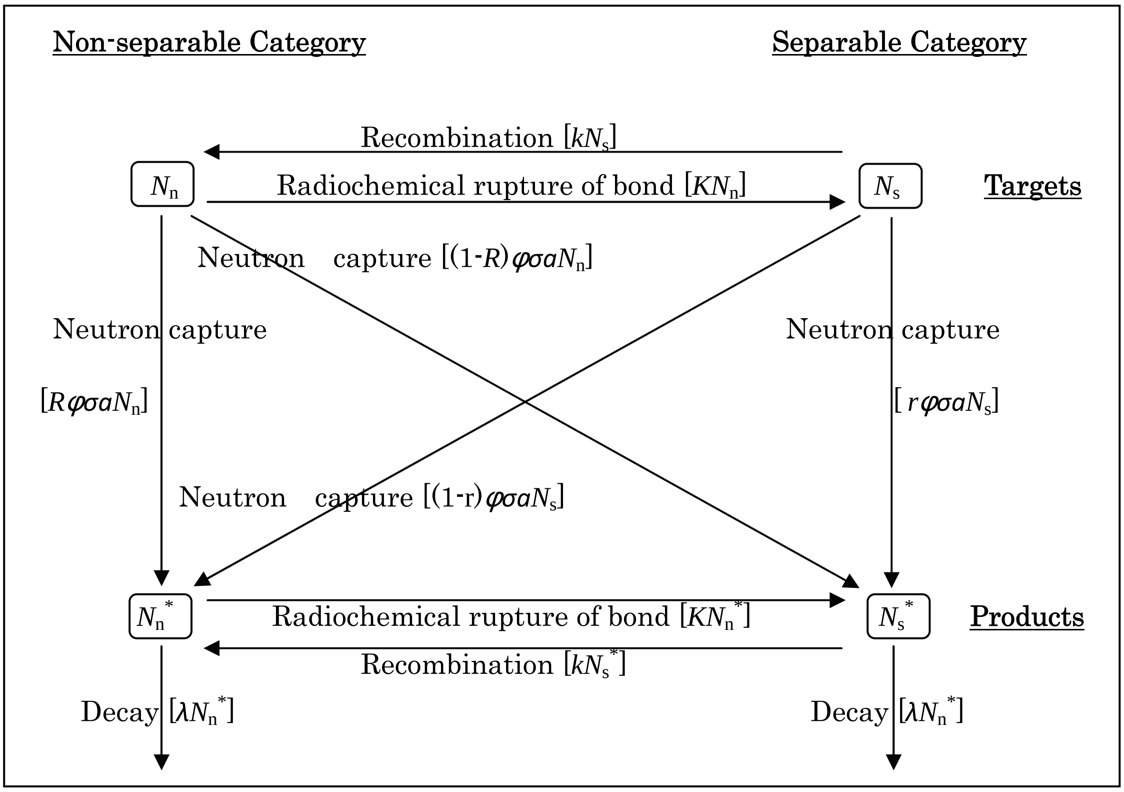


Figure A.5-1. Flow diagram of target and product atoms during neutron irradiation

Non-separable or separable state: chemical state of an interested atom from which the atom cannot or can be selectively separated, respectively. Subscript-n, subscript-s, superscript-* and no superscript for N denote non-separable, separable, product and target, respectively.

N: Numbers of atoms interested

φ, σ, a, λ: neutron flux, microscopic neutron capture cross section for the production, abundance of target isotope giving the product, and decay constant of product, respectively

K: probability that an atom at the non-separable state transits to separable state per unit time by radiochemical rupture of its chemical bond

k: probability that an atom at the separable state transits to non-separable state per unit time by recombination

R: probability that a product atom captured a neutron at the non-separable state is retained at the same state (retention factor)

r: probability that a product atom captured a neutron at the separable state remains at the same state (remaining factor)

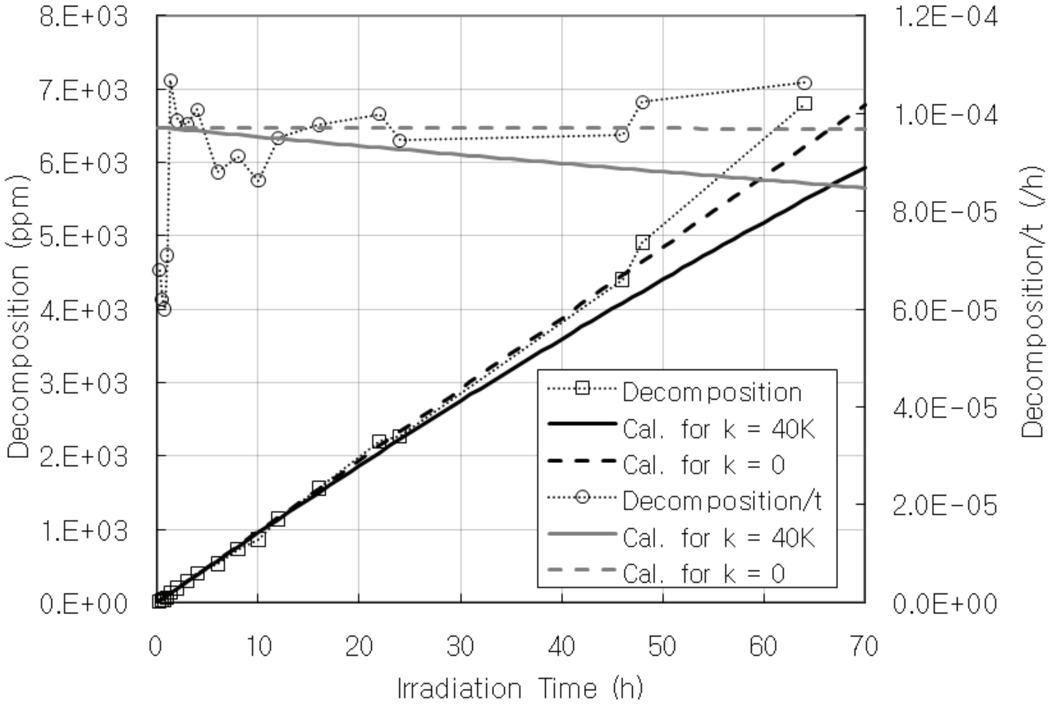


Figure A.5-2. Decomposition of K_2BrO_3 versus neutron irradiation time

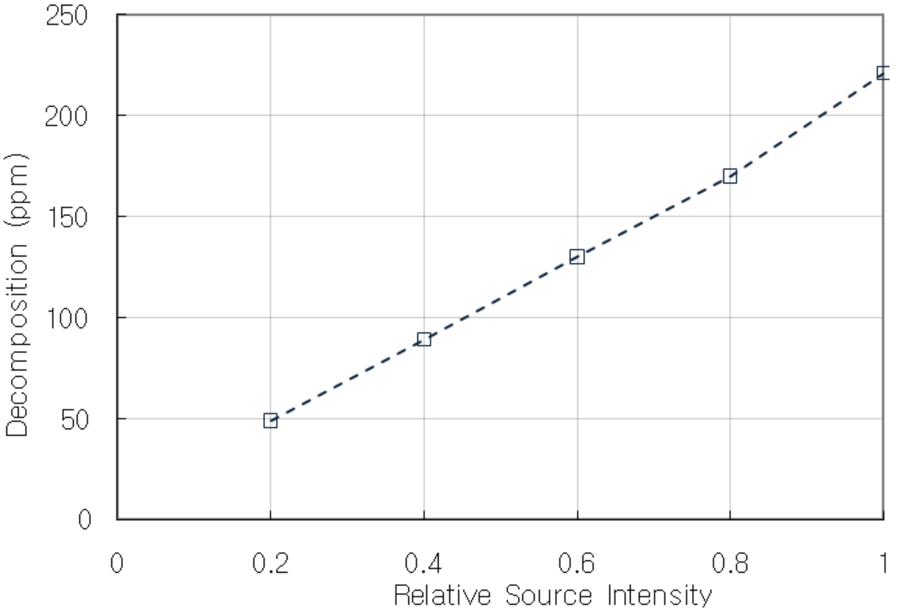


Figure A.5-3. Decomposition of K_2BrO_3 versus relative intensity of neutron source for 2 h irradiations

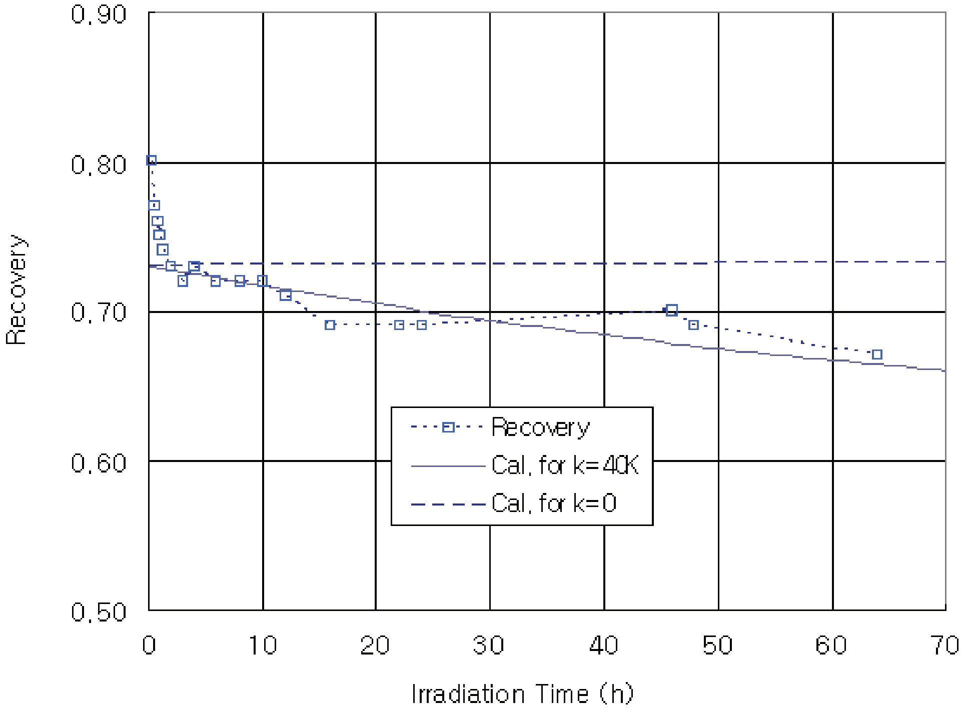


Figure A.5-4. Trends of ^{82}Br recovery at separable state from neutron irradiation of K_2BrO_3

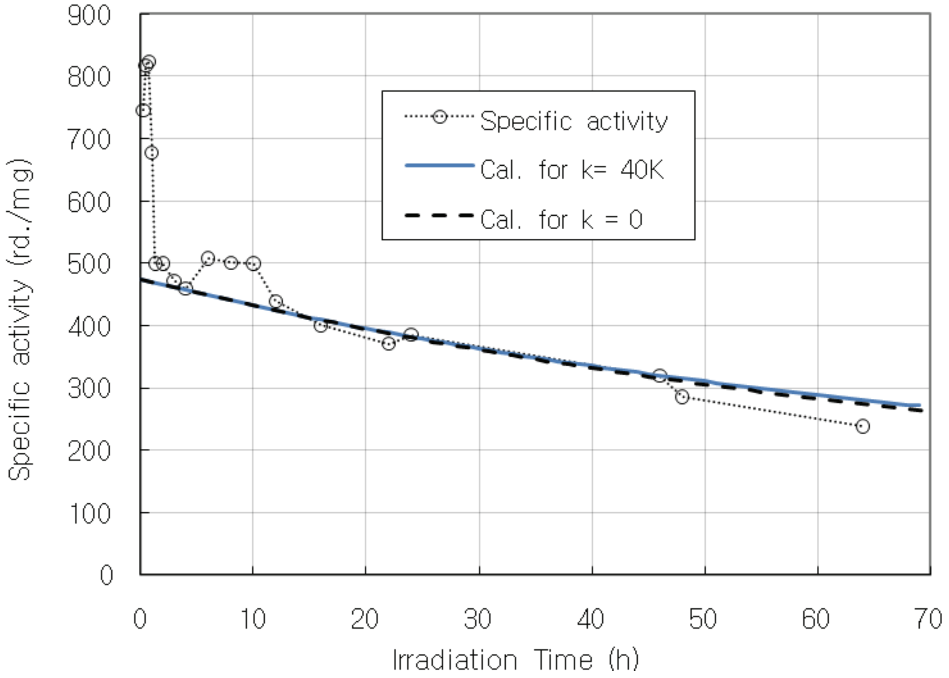


Figure A.5-5. Specific activity of ^{82}Br at separable state for neutron irradiation of K_2BrO_3

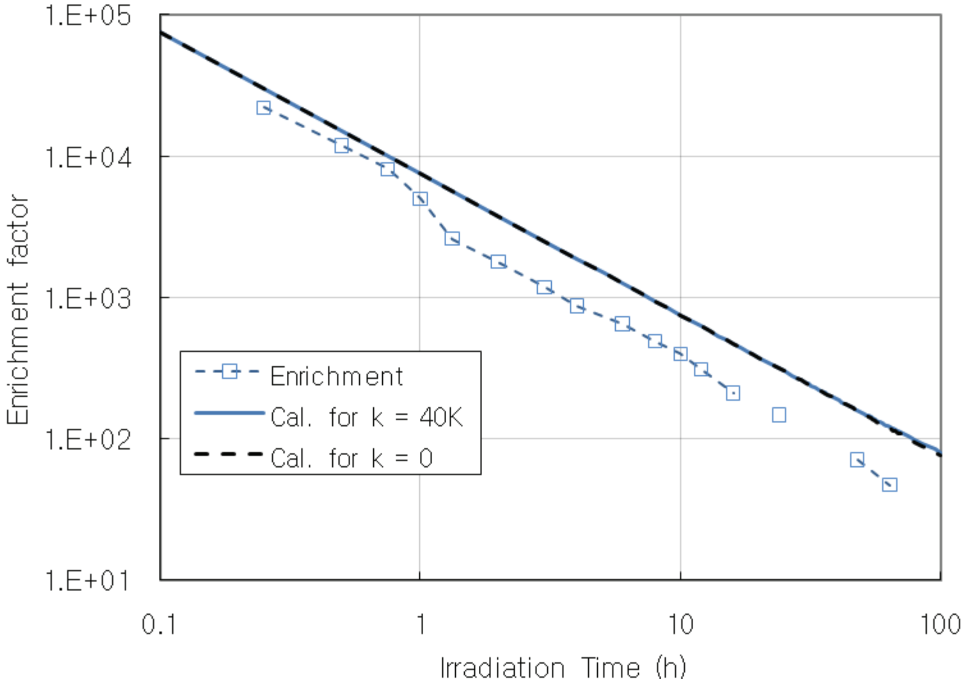


Figure A.5-6. ^{82}**Br enrichment factor by neutron irradiation of** K_2BrO_3

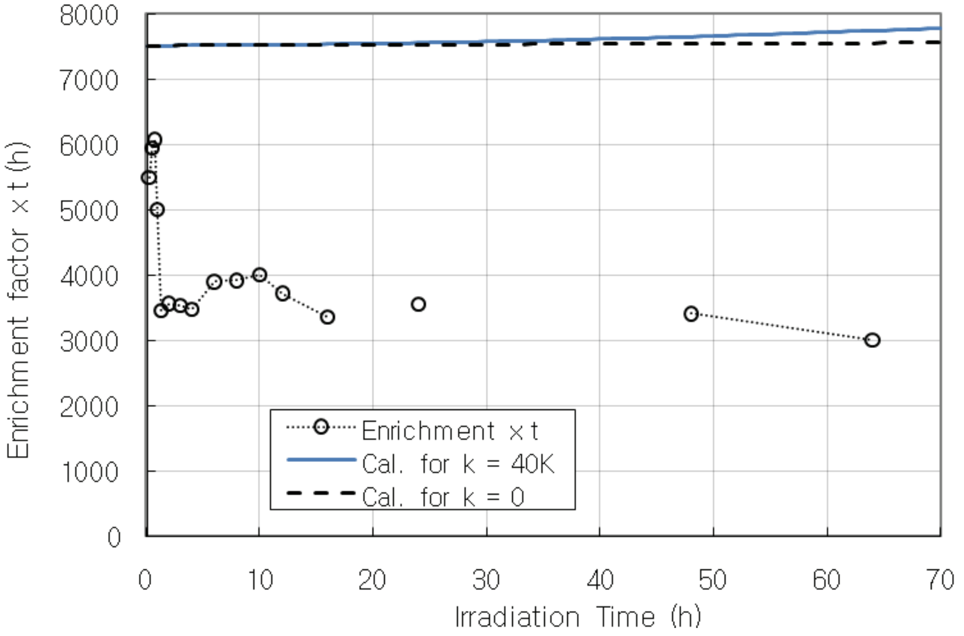


Figure A.5-7. Product of ^{82}**Br enrichment factor and irradiation time for neutron irradiation of** K_2BrO_3

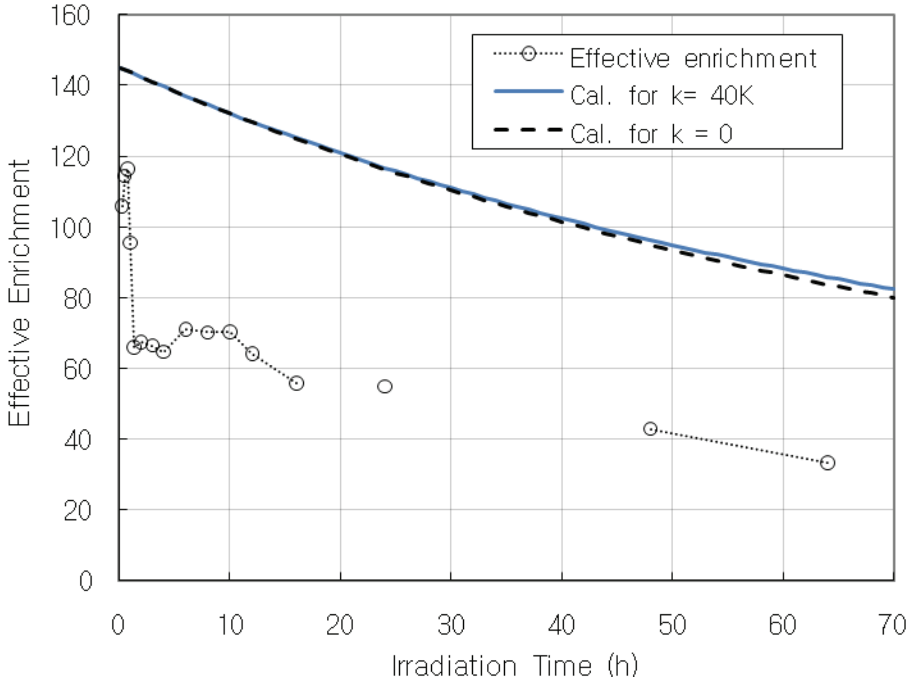


Figure A.5-8. Effective enrichment of ^{82}Br for neutron irradiation of K_2BrO_3

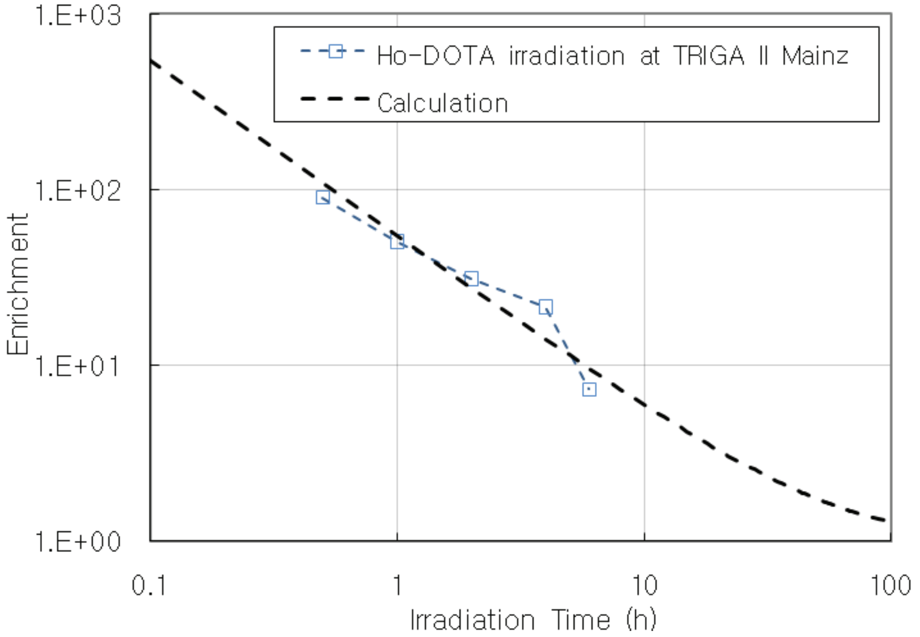


Figure A.5-9. Comparison of calculated and measured enrichment factor for Ho-DOTA irradiation at $4x10^{12}$ n/cm^{2}s neutron flux of TRIGA II Mainz

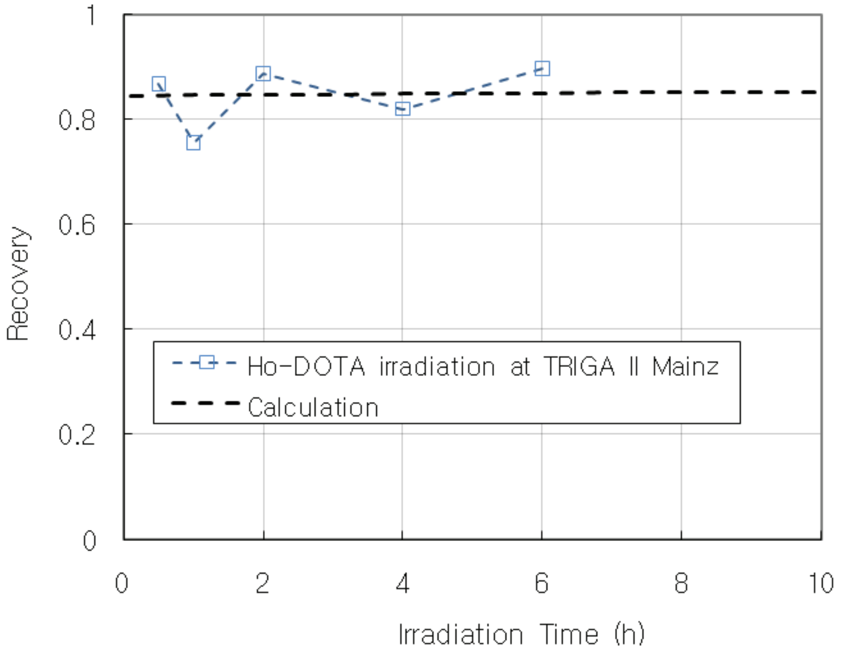


Figure A.5-10. Comparison of calculated and measured recovery for Ho-DOTA irradiation at 4x10^{12} n/cm^{2}s neutron flux of TRIGA II Mainz

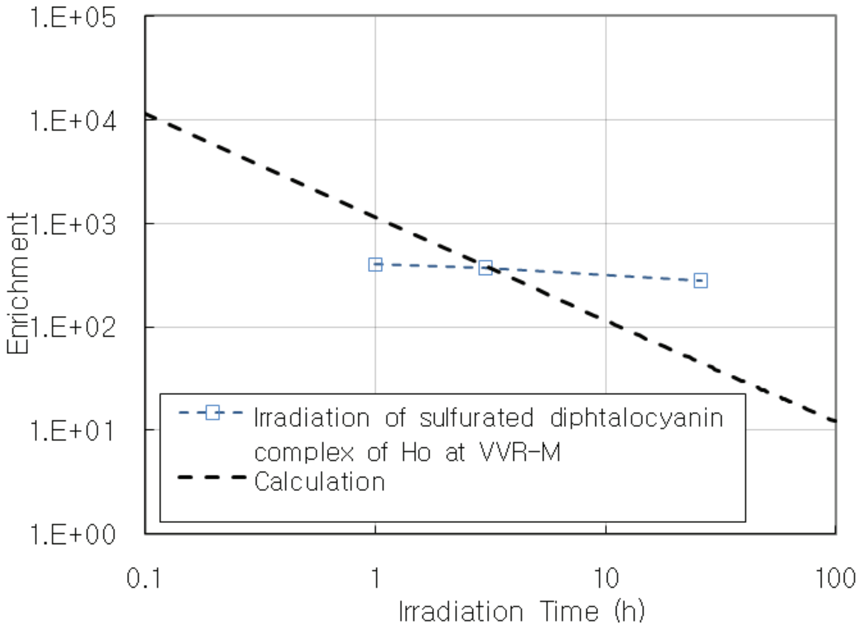


Figure A.5-11. Comparison of calculated and measured enrichment factor for Shapkin et al for irradiation of sulfurated diphtalocyanin complex of ^{165}Ho at 5x10^{13} n/cm^{2}s neutron flux of VVR-M reactor

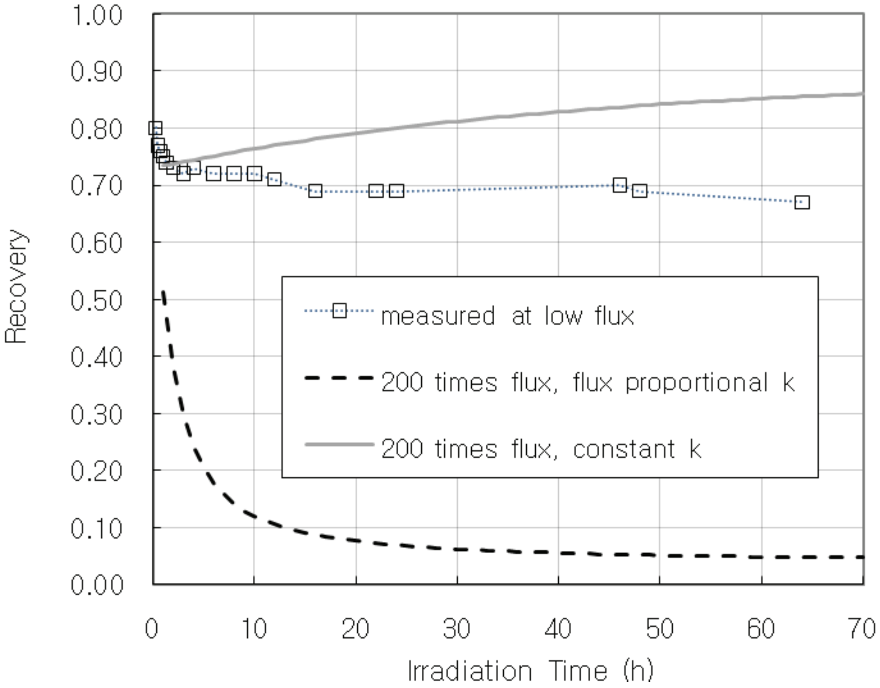


Figure A.5-12. Predicted recovery for irradiation of K_2BrO_3 at high neutron flux (*r* = 1 for prediction)

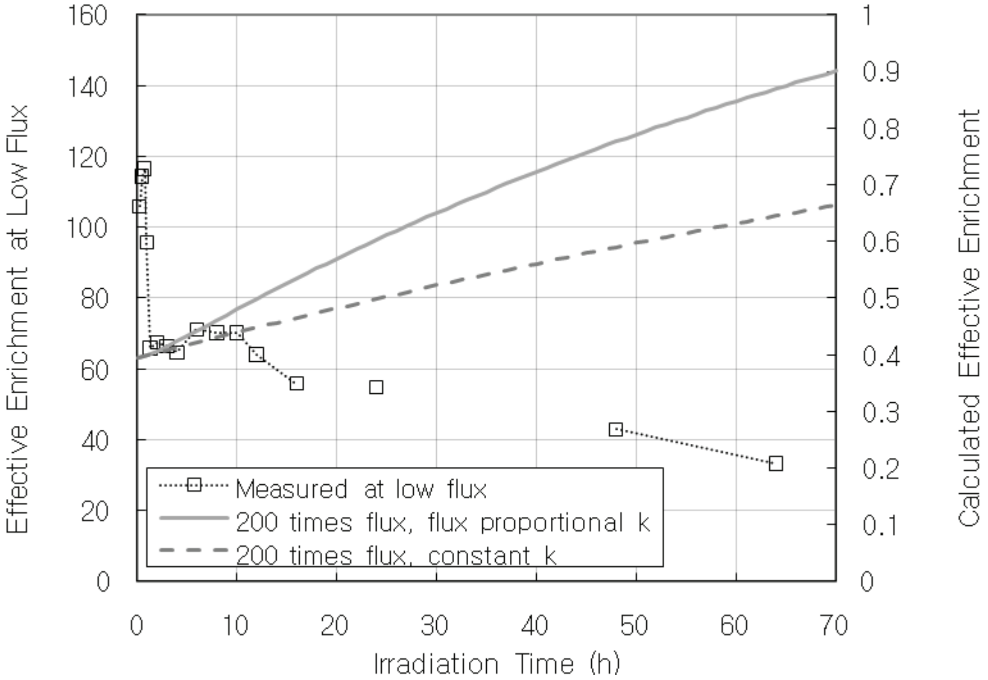


Figure A.5-13. Predicted effective enrichment for irradiation of K_2BrO_3 at high neutron flux (*r* = 1 for prediction)

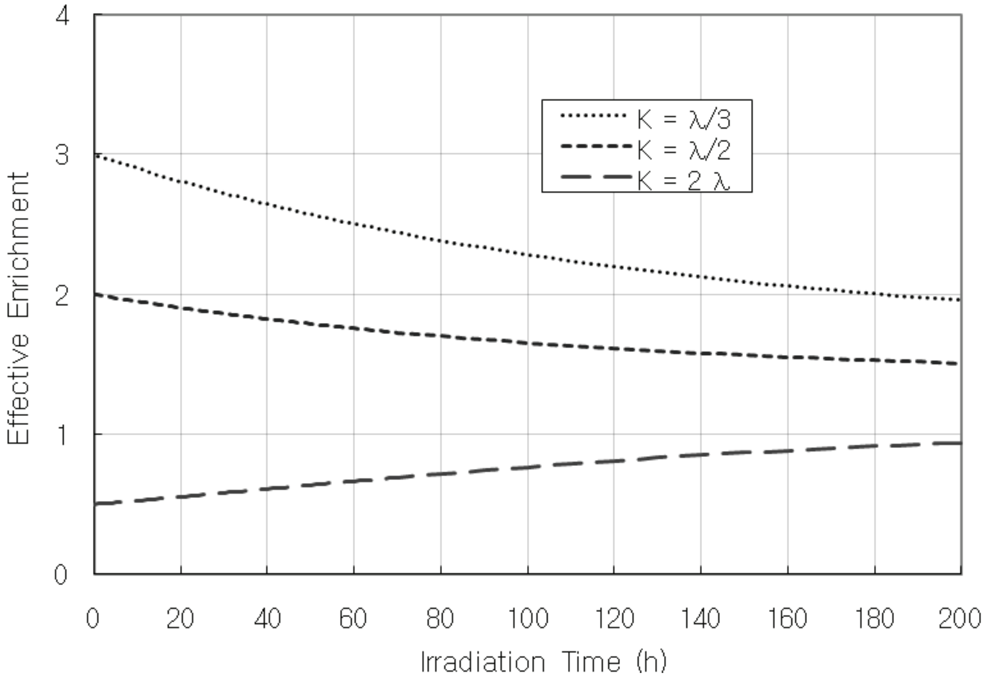


Figure A.5-14. Effective enrichment of 99Mo depending on the ratio between decomposition factor *f* and decay constant λ when *k* = *R* = 0 and *r* = 1

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国際単位系（SI）

表１．SI 基本単位

基本量	SI 基本単位	
	名称	記号
長さ	メートル	m
質量	キログラム	kg
時間	秒	s
電流	アンペア	A
熱力学温度	ケルビン	K
物質量	モル	mol
光度	カンデラ	cd

表２．基本単位を用いて表されるSI組立単位の例

組立量	SI 基本単位	
	名称	記号
面積	平方メートル	$\mathrm{m^2}$
体積	立法メートル	$\mathrm{m^3}$
速さ，速度	メートル毎秒	m/s
加速度	メートル毎秒毎秒	$\mathrm{m/s^2}$
波数	毎メートル	$\mathrm{m^{-1}}$
密度，質量密度	キログラム毎立方メートル	$\mathrm{kg/m^3}$
面積密度	キログラム毎平方メートル	$\mathrm{kg/m^2}$
比体積	立方メートル毎キログラム	$\mathrm{m^3/kg}$
電流密度	アンペア毎平方メートル	$\mathrm{A/m^2}$
磁界の強さ	アンペア毎メートル	A/m
量濃度(a)，濃度	モル毎立方メートル	$\mathrm{mol/m^3}$
質量濃度	キログラム毎立法メートル	$\mathrm{kg/m^3}$
輝度	カンデラ毎平方メートル	$\mathrm{cd/m^2}$
屈折率(b)	（数字の） 1	1
比透磁率(b)	（数字の） 1	1

(a) 量濃度（amount concentration）は臨床化学の分野では物質濃度（substance concentration）ともよばれる。
(b) これらは無次元量あるいは次元１をもつ量であるが、そのことを表す単位記号である数字の１は通常は表記しない。

表３．固有の名称と記号で表されるSI組立単位

組立量	SI 組立単位			
	名称	記号	他のSI単位による表し方	SI基本単位による表し方
平面角	ラジアン(b)	rad	1 (b)	m/m
立体角	ステラジアン(b)	sr(c)	1 (b)	$\mathrm{m^2/m^2}$
周波数	ヘルツ(d)	Hz		$\mathrm{s^{-1}}$
力	ニュートン	N		$\mathrm{m\,kg\,s^{-2}}$
圧力，応力	パスカル	Pa	$\mathrm{N/m^2}$	$\mathrm{m^{-1}\,kg\,s^{-2}}$
エネルギー，仕事，熱量	ジュール	J	N m	$\mathrm{m^2\,kg\,s^{-2}}$
仕事率，工率，放射束	ワット	W	J/s	$\mathrm{m^2\,kg\,s^{-3}}$
電荷，電気量	クーロン	C		s A
電位差（電圧），起電力	ボルト	V	W/A	$\mathrm{m^2\,kg\,s^{-3}\,A^{-1}}$
静電容量	ファラド	F	C/V	$\mathrm{m^{-2}\,kg^{-1}\,s^4\,A^2}$
電気抵抗	オーム	Ω	V/A	$\mathrm{m^2\,kg\,s^{-3}\,A^{-2}}$
コンダクタンス	ジーメンス	S	A/V	$\mathrm{m^{-2}\,kg^{-1}\,s^3\,A^2}$
磁束	ウエーバ	Wb	Vs	$\mathrm{m^2\,kg\,s^{-2}\,A^{-1}}$
磁束密度	テスラ	T	$\mathrm{Wb/m^2}$	$\mathrm{kg\,s^{-2}\,A^{-1}}$
インダクタンス	ヘンリー	H	Wb/A	$\mathrm{m^2\,kg\,s^{-2}\,A^{-2}}$
セルシウス温度	セルシウス度(e)	℃		K
光束	ルーメン	lm	cd sr(c)	cd
照度	ルクス	lx	$\mathrm{lm/m^2}$	$\mathrm{m^{-2}\,cd}$
放射性核種の放射能(f)	ベクレル(d)	Bq		$\mathrm{s^{-1}}$
吸収線量, 比エネルギー分与, カーマ	グレイ	Gy	J/kg	$\mathrm{m^2\,s^{-2}}$
線量当量, 周辺線量当量, 方向性線量当量, 個人線量当量	シーベルト(g)	Sv	J/kg	$\mathrm{m^2\,s^{-2}}$
酸素活性	カタール	kat		$\mathrm{s^{-1}\,mol}$

(a)SI接頭語は固有の名称と記号を持つ組立単位と組み合わせても使用できる。しかし接頭語を付した単位はもはやコヒーレントではない。
(b)ラジアンとステラジアンは数字の１に対する単位の特別な名称で、量についての情報をつたえるために使われる。実際には、使用する時には記号rad及びsrが用いられるが、習慣として組立単位としての記号である数字の１は明示されない。
(c)測光学ではステラジアンという名称と記号srを単位の表し方の中に、そのまま維持している。
(d)ヘルツは周期現象についてのみ、ベクレルは放射性核種の統計的過程についてのみ使用される。
(e)セルシウス度はケルビンの特別な名称で、セルシウス温度を表すために使用される。セルシウス度とケルビンの単位の大きさは同一である。したがって、温度差や温度間隔を表す数値はどちらの単位で表しても同じである。
(f)放射性核種の放射能（activity referred to a radionuclide）は、しばしば誤った用語で”radioactivity”と記される。
(g)単位シーベルト（PV,2002,70,205）についてはCIPM勧告2（CI-2002）を参照。

表４．単位の中に固有の名称と記号を含むSI組立単位の例

組立量	SI 組立単位		
	名称	記号	SI 基本単位による表し方
粘度	パスカル秒	Pa s	$\mathrm{m^{-1}\,kg\,s^{-1}}$
力のモーメント	ニュートンメートル	N m	$\mathrm{m^2\,kg\,s^{-2}}$
表面張力	ニュートン毎メートル	N/m	$\mathrm{kg\,s^{-2}}$
角速度	ラジアン毎秒	rad/s	$\mathrm{m\,m^{-1}\,s^{-1}=s^{-1}}$
角加速度	ラジアン毎秒毎秒	$\mathrm{rad/s^2}$	$\mathrm{m\,m^{-1}\,s^{-2}=s^{-2}}$
熱流密度，放射照度	ワット毎平方メートル	$\mathrm{W/m^2}$	$\mathrm{kg\,s^{-3}}$
熱容量，エントロピー	ジュール毎ケルビン	J/K	$\mathrm{m^2\,kg\,s^{-2}\,K^{-1}}$
比熱容量，比エントロピー	ジュール毎キログラム毎ケルビン	J/(kg K)	$\mathrm{m^2\,s^{-2}\,K^{-1}}$
比エネルギー	ジュール毎キログラム	J/kg	$\mathrm{m^2\,s^{-2}}$
熱伝導率	ワット毎メートル毎ケルビン	W/(m K)	$\mathrm{m\,kg\,s^{-3}\,K^{-1}}$
体積エネルギー	ジュール毎立方メートル	$\mathrm{J/m^3}$	$\mathrm{m^{-1}\,kg\,s^{-2}}$
電界の強さ	ボルト毎メートル	V/m	$\mathrm{m\,kg\,s^{-3}\,A^{-1}}$
電荷密度	クーロン毎立方メートル	$\mathrm{C/m^3}$	$\mathrm{m^{-3}\,sA}$
表面電荷	クーロン毎平方メートル	$\mathrm{C/m^2}$	$\mathrm{m^{-2}\,sA}$
電束密度，電気変位	クーロン毎平方メートル	$\mathrm{C/m^2}$	$\mathrm{m^{-2}\,sA}$
誘電率	ファラド毎メートル	F/m	$\mathrm{m^{-3}\,kg^{-1}\,s^4\,A^2}$
透磁率	ヘンリー毎メートル	H/m	$\mathrm{m\,kg\,s^{-2}\,A^{-2}}$
モルエネルギー	ジュール毎モル	J/mol	$\mathrm{m^2\,kg\,s^{-2}\,mol^{-1}}$
モルエントロピー, モル熱容量	ジュール毎モル毎ケルビン	J/(mol K)	$\mathrm{m^2\,kg\,s^{-2}\,K^{-1}\,mol^{-1}}$
照射線量（Ｘ線及びγ線）	クーロン毎キログラム	C/kg	$\mathrm{kg^{-1}\,sA}$
吸収線量率	グレイ毎秒	Gy/s	$\mathrm{m^2\,s^{-3}}$
放射強度	ワット毎ステラジアン	W/sr	$\mathrm{m^4\,m^{-2}\,kg\,s^{-3}=m^2\,kg\,s^{-3}}$
放射輝度	ワット毎平方メートル毎ステラジアン	$\mathrm{W/(m^2\,sr)}$	$\mathrm{m^2\,m^{-2}\,kg\,s^{-3}=kg\,s^{-3}}$
酵素活性濃度	カタール毎立方メートル	$\mathrm{kat/m^3}$	$\mathrm{m^{-3}\,s^{-1}\,mol}$

表５．SI 接頭語

乗数	接頭語	記号	乗数	接頭語	記号
10^{24}	ヨタ	Y	10^{-1}	デシ	d
10^{21}	ゼタ	Z	10^{-2}	センチ	c
10^{18}	エクサ	E	10^{-3}	ミリ	m
10^{15}	ペタ	P	10^{-6}	マイクロ	µ
10^{12}	テラ	T	10^{-9}	ナノ	n
10^{9}	ギガ	G	10^{-12}	ピコ	p
10^{6}	メガ	M	10^{-15}	フェムト	f
10^{3}	キロ	k	10^{-18}	アト	a
10^{2}	ヘクト	h	10^{-21}	ゼプト	z
10^{1}	デカ	da	10^{-24}	ヨクト	y

表６．SIに属さないが、SIと併用される単位

名称	記号	SI 単位による値
分	min	1 min=60s
時	h	1h =60 min=3600 s
日	d	1 d=24 h=86 400 s
度	°	1°=(π/180) rad
分	’	1’=(1/60)°=(π/10800) rad
秒	”	1”=(1/60)’=(π/648000) rad
ヘクタール	ha	$\mathrm{1ha=1hm^2=10^4m^2}$
リットル	L，l	$\mathrm{1L=1l=1dm^3=10^3cm^3=10^{-3}m^3}$
トン	t	$\mathrm{1t=10^3\,kg}$

表７．SIに属さないが、SIと併用される単位で、SI単位で表される数値が実験的に得られるもの

名称	記号	SI 単位で表される数値
電子ボルト	eV	$\mathrm{1eV=1.602\,176\,53(14)\times10^{-19}J}$
ダルトン	Da	$\mathrm{1Da=1.660\,538\,86(28)\times10^{-27}kg}$
統一原子質量単位	u	1u=1 Da
天文単位	ua	$\mathrm{1ua=1.495\,978\,706\,91(6)\times10^{11}m}$

表８．SIに属さないが、SIと併用されるその他の単位

名称	記号	SI 単位で表される数値
バール	bar	$\mathrm{1\,bar=0.1MPa=100kPa=10^5Pa}$
水銀柱ミリメートル	mmHg	1mmHg=133.322Pa
オングストローム	Å	$\mathrm{1\,Å=0.1nm=100pm=10^{-10}m}$
海里	M	1 M=1852m
バーン	b	$\mathrm{1\,b=100fm^2=(10^{-12}cm)2=10^{-28}m^2}$
ノット	kn	1 kn=(1852/3600)m/s
ネーパ	Np	SI単位との数値的な関係は、対数量の定義に依存。
ベル	B	
デジベル	dB	

表９．固有の名称をもつCGS組立単位

名称	記号	SI 単位で表される数値
エルグ	erg	$\mathrm{1\,erg=10^{-7}\,J}$
ダイン	dyn	$\mathrm{1\,dyn=10^{-5}N}$
ポアズ	P	$\mathrm{1\,P=1\,dyn\,s\,cm^{-2}=0.1Pa\,s}$
ストークス	St	$\mathrm{1\,St=1cm^2\,s^{-1}=10^{-4}m^2\,s^{-1}}$
スチルブ	sb	$\mathrm{1\,sb=1cd\,cm^{-2}=10^4cd\,m^{-2}}$
フォト	ph	$\mathrm{1\,ph=1cd\,sr\,cm^{-2}\,10^4lx}$
ガル	Gal	$\mathrm{1\,Gal=1cm\,s^{-2}=10^{-2}ms^{-2}}$
マクスウェル	Mx	$\mathrm{1\,Mx=1G\,cm^2=10^{-8}Wb}$
ガウス	G	$\mathrm{1\,G=1Mx\,cm^{-2}=10^{-4}T}$
エルステッド(c)	Oe	$\mathrm{1\,Oe} \triangleq (10^3/4\pi)\mathrm{A\,m^{-1}}$

(c) ３元系のCGS単位系とSIでは直接比較できないため、等号「 ≙ 」は対応関係を示すものである。

表10．SIに属さないその他の単位の例

名称	記号	SI 単位で表される数値
キュリー	Ci	$\mathrm{1\,Ci=3.7\times10^{10}Bq}$
レントゲン	R	$\mathrm{1\,R=2.58\times10^{-4}C/kg}$
ラド	rad	$\mathrm{1\,rad=1cGy=10^{-2}Gy}$
レム	rem	$\mathrm{1\,rem=1\,cSv=10^{-2}Sv}$
ガンマ	γ	1 γ =1 nT=10-9T
フェルミ		1フェルミ=1 fm=10-15m
メートル系カラット		1メートル系カラット = 200 mg = 2×10-4kg
トル	Torr	1 Torr = (101 325/760) Pa
標準大気圧	atm	1 atm = 101 325 Pa
カロリー	cal	1cal=4.1858J（「15℃」カロリー），4.1868J（「IT」カロリー）4.184J（「熱化学」カロリー）
ミクロン	µ	$\mathrm{1\,\mu=1\mu m=10^{-6}m}$

（第8版，2006年改訂）