Nuclear Laboratory 2: Radionuclide Generator

Why do we need a radionuclide generator?

Short-lived radionuclides are often the agents of choice in nuclear medicine because they permit the use of ample radioactivity while keeping the absorbed dose to the patient within acceptable limits. In general, however, the use of short-lived radionuclides entails many problems that stem from their fast decay. For example, the time available for processing, transportation, storage and dispensing is very limited and is often insufficient to assure quality in labeling and in radionuclidic purity. A generator solves some of the problems associated with the transportation of short-lived radionuclides.

What is a radionuclide generator?

Radionuclide generators are devices that produce a useful short-lived medical radionuclide (known as “daughter”) from the radioactive transformation of a non-medical long-lived radionuclide (called a “parent”). By having a supply of parent on hand at a facility, the daughter is continually generated on site. The generator permits ready separation of the daughter radionuclide from the parent. Once separation occurs, the generator starts generating more daughter that can be again separated in sufficient quantity at a later time.

For generator systems to be practical, the parent must have a relatively long half-life compared to that of the daughter, and the generator device (often referred as a "cow") must provide for repeated separations of the daughter product. This separation process is called an elution (colloquially it is also referred to as a "milking"). The example of outstanding importance is the $^{99}\text{Mo} - ^{99m}\text{Tc}$ (“Moly”) generator. $^{99}\text{Mo}$ has a half-life of 66 hours and can be easily transported over long distances without serious loss of activity. Its short half-life decay product, technetium-99m, can be extracted and used at the remote facility. The useful life of a $^{99}\text{Mo} - ^{99m}\text{Tc}$ generator is about 3 parent half lives, or approximately one week.

How do we get Tc-99m from a cow?

A technetium-99m generator, or colloquially a technetium cow, is a device used to extract the metastable isotope $^{99m}\text{Tc}$ from a source of decaying molydenum-99. Mo-99 used in these generators is produced either by neutron irradiation of Mo-98 ($^{98}\text{Mo} + n \rightarrow ^{99}\text{Mo} + \gamma$) or by fission of U-235 (Uranium-235) in a nuclear reactor.

$$\text{(e.g. } ^{235}\text{U} + ^{1}\text{n}_{\text{thermal}} \rightarrow ^{236}\text{U} \rightarrow ^{99}\text{Mo} + ^{134}\text{Sn} + ^{3}\text{n})$$

Most commercial $^{99}\text{Mo} - ^{99m}\text{Tc}$ generators use column chromatography, in which $^{99}\text{Mo}$ is adsorbed onto acid alumina (Al$_2$O$_3$). Pulling or pushing normal saline solution through...
the column of immobilized $^{99}$Mo elutes the soluble $^{99m}$Tc, resulting in a saline solution containing radioactive $^{99m}$Tc and a good amount of Tc-99. The Tc-99 is a carrier that is, for all practical purposes, stable. Chemically, it behaves identically to Tc-99. Since Tc-99 cannot be separated from $^{99m}$Tc, it is a by-product that is included with the isomer but which has no medical advantage. Also included in the elution will be a small amount of Mo-99 and some Aluminum ions. These latter two substances are contaminants, the quantities of which must be limited for the protection of the patient.

The process of milking the cow.

The heart of the generator consists of a ceramic column with $^{99}$Mo adsorbed onto its top surface. A solution called an **eluent** is passed through the column and reacts chemically with any Technetium. The arrangement shown in figure 1 below is called a positive pressure system where the eluent is forced through the ceramic column by a pressure, slightly above atmospheric pressure, in the eluent vial.

![Figure 1](image)

![Figure 2](image)

The ceramic column and collection vials need to be surrounded by lead shielding for radiation protection purposes (Figure 2). In addition all components are produced and maintained in a sterile condition since the collected solution will be administered to patients.

Physics and chemistry of nuclear cows.

As the parent, Mo-99, decays, the concentration of the daughter, Tc-99m, increases in the column. Tc-99m reaches a maximum after about 24 hours (Figure 3). Because the daughter element is chemically different from its parent, it is not bound to the column, and it accumulates in the solvent. When the column is flushed with aqueous sodium...
chloride, it yields a solution containing sodium pertechnetate, NaTcO₄. After flushing, the concentration of Tc-99m is largely depleted from the column but immediately starts to increase again. This increase of daughter activity continues but ultimately begins to slow. Eventually the daughter activity is produced at a rate that nearly equals that at which it decays. When the ratio of the rate of production of the daughter and rate of decay of the daughter stabilize, the system is said to be in equilibrium. Figure 4 demonstrates in simple terms the Mo-99-Tc-99m radionuclide generator in which the half-life of the parent nuclide is much longer than that of the daughter nuclide. About 50% of the equilibrium activity is reached within one daughter half-life, 75% within two daughter half-lives and so on. It takes about 4 daughter half-lives to reach equilibrium with the parent. Once equilibrium has been achieved between the parent and daughter radioactivities, it can be disturbed only by chemical separation. Removing the daughter nuclide from the generator ("milking" the generator) is reasonably done every 6 hours or, at most, twice daily in a Mo-99-Tc-99m generator. Because the half-life of Mo-99 is 66 hours or slightly less than 3 days, the supply of parent product will deplete to insufficient levels in roughly one week and must be replaced with a fresh system.

Figure 3
Regulatory requirements on quality control of generators.

State and federal regulations describe quality control tests and the frequency with which they must be performed to ensure that the eluate from the radionuclide generator is suitable for use. Moly generators yield a number of possible contaminants, mainly breakthrough of Mo-99 and aluminum ion. End users must check for these two before using any generator.

### CLASSIFICATION OF IMPURITIES

<table>
<thead>
<tr>
<th>Type</th>
<th>Effect</th>
<th>Limits</th>
<th>Detection Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radionuclidic:</td>
<td>Radiation Dose</td>
<td>&lt; 0.15 uCi /mCi of Tc-99m at time of administration</td>
<td>Dose Calibrator</td>
</tr>
<tr>
<td>Mo-99</td>
<td>Poor Image Quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical:</td>
<td>Poor Image Quality</td>
<td></td>
<td>Colorimetric</td>
</tr>
<tr>
<td>Al&lt;sup&gt;3+&lt;/sup&gt;</td>
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Mo-99 contamination is usually caused by migration of the Mo-99 in the alumina column with successive elutions. The amount of Mo-99 which is eluted with the Tc-99m should be as small as possible because the contamination by the longer lived radionuclide increases the radiation dose without providing any benefit to the patient.
Texas and the NRC regulations state if a licensee directly uses a moly generator then the
licensee (i.e., you) must measure and document the Mo-99 concentration of the first elute
after receipt of a generator. The licensee must not administer to humans a
radiopharmaceutical containing more than 0.15 uCi of Mo-99 per millicurie of Tc-99m.
Now, consider the fact that Tc-99m will decrease far more rapidly than the small amount
of Mo-99. This fact implies that the ration of Mo-99 contaminant to Tc-99m will increase
fairly rapidly, nearly by a factor of two every six hours. Since most radiopharmaceuticals
expire 12 hours after formulation, the moly assay at time of elution must take this 12-
hour interval into consideration by assuring that the limit will not be exceeded 12 hours
later. That is, the Mo-99 breakthrough at the time of elution should be about one-fourth
the allowed limit, or no more than 0.0398 uCi of Mo-99 per mCi of Tc-99m.

1. **Mo-99 Breakthrough**: Mo-99 breakthrough in a vial of Tc-99m eluate is assayed
directly in your dose calibrator using a special lead pig supplied with the calibrator. Why
is this necessary? ____________________________________________________________

Read this Information Notice:

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UNITED STATES
NUCLEAR REGULATORY COMMISSION
OFFICE OF FEDERAL AND STATE MATERIALS
AND ENVIRONMENTAL MANAGEMENT PROGRAMS
WASHINGTON, D.C. 20555

January 12, 2009

NRC INFORMATION NOTICE 2008-22: MOLYBDENUM-99 BREAKTHROUGH IN
MOLYBDENUM-99/TECHNETIUM-99M GENERATORS

ADDRESSEES

All U.S. Nuclear Regulatory Commission (NRC) medical, radiopharmacy, molybdenum-
99/technetium-99m generator (generator) manufacturer, and master material licensees
authorized to manufacture or use generators. All Agreement State radiation control
program directors and State liaison officers.

PURPOSE

The NRC is issuing this information notice (IN) to inform addressees about elevated
molybdenum-99 (Mo-99) breakthrough following the elution of generators. The NRC
expects that recipients will review the information for applicability to their facilities and
consider appropriate actions. However, the suggested actions contained in the IN do not
constitute NRC requirements; therefore, the NRC requires no specific action or written
response.
The NRC is providing this IN to the Agreement States for their information, and for distribution to their medical, generator manufacturer, and radiopharmacy licensees, as appropriate.

DESCRIPTION OF CIRCUMSTANCES

The NRC has become aware of an unusual number of reports made by medical licensees to a generator manufacturer during the period of October 2006 through February 2007, and in January 2008, concerning increased concentrations of Mo-99 in generator eluates. A number of licensees reported that their generators have failed the Mo-99 breakthrough tests, i.e., the measurement exceeded the regulatory limit in Title 10 of the Code of Federal Regulations, Part 35, Section 35.204 (10 CFR 35.204), “Permissible molybdenum-99, strontium-82, and strontium-85 concentrations,” of 0.15 kilobecquerel of Mo-99 per megabecquerel of Tc-99m (0.15 microcurie (µCi) of Mo-99 per millicurie (mCi) of technetium-99m (Tc-99m)).

Some licensees reported measurements for Mo-99 breakthrough that failed at the first elution, while other reported Mo-99 measurements were within regulatory limit at the first elution, but failure during subsequent elutions. The majority of the reports involved concentrations of Mo-99 that did not exceed the regulatory limit at the time of elution but, due to the decay rate of Tc-99m, the ratio of Mo-99 to Tc-99m would have exceeded the regulatory limit of 0.15 µCi of Mo-99 per mCi of Tc-99m before the 12 hours post elution expiration time stated in the generator package insert.

DISCUSSION

10 CFR Part 35, Section 35.204(b) requires licensees to measure the Mo-99 concentration of the first eluate after receipt of a generator. However, package inserts that accompanied each generator recommended that customers test each elution for Mo-99 breakthrough. These recent occurrences of Mo-99 breakthrough, especially those measurements that failed during subsequent elutions, emphasize the importance of following the manufacturer’s package insert and testing each elution for breakthrough.

The NRC concluded that the safety significance of administering Mo-99 at the concentrations that were reported to the manufacturer between October 2006 and February 2007, and in January 2008, was low. However, the administration of higher levels of molybdenum-99 could potentially affect health and safety, as well as have an adverse effect on nuclear medicine image quality and medical diagnosis.

The NRC staff will consider initiating a rulemaking to require Mo-99 breakthrough measurements of each elution to demonstrate compliance with the limit of 0.15 µCi of Mo-99 per mCi of Tc-99m, rather than just the first elution. The NRC will also consider initiating a rulemaking to require reporting of noncompliance with the concentration limit. In the interim, the NRC strongly encourages all licensees who use a Mo-99/Tc-99m generator to measure each eluate for Mo-99 breakthrough before Tc-99m is administered to humans, and to report any concentrations that exceed the regulatory limits described in 10 CFR 35.204(a) to the generator manufacturer. NRC also encourages voluntary reporting by each generator manufacturer to the NRC of notifications provided to them.
by medical licensees who have measured concentrations of Mo-99 in the generator eluate that exceed the regulatory limits described in 10 CFR 35.204(a).

CONTACT

This IN requires no specific action or written response. Please direct any questions to the technical contact(s) listed below.

/Terrence Reis for /
Robert J. Lewis, Director
Division of Materials Safety and State Agreements
Office of Federal and State Materials and Environmental Management Programs

Tc-99m is assayed directly in the plastic sleeve in your dose calibrator. Activity (uCi) of Mo-99 is divided by activity (mCi) of Tc-99m to obtain the ratio. If this ratio is <0.15 \( \mu \text{Ci Mo-99 per mCi of Tc-99m} \) at time of injection, the generator eluate has passed the Mo-99 Breakthrough Test. As a rule of thumb, if the ratio is <0.0398 at time of elution, the material will be suitable for injection for at least 12 hours.

2. **Aluminum Ion Breakthrough**: \( \text{Al}^{3+} \) ion is measured colorimetrically. A drop of the eluate is placed on one end of a special test paper. A drop of a standard solution of \( \text{Al}^{3+} \) with concentration of 10 ppm, is placed on the other end of the test strip. If the color at the center of the drop of eluate is less red than that of the standard solution, the eluate has passed the Aluminum Ion Breakthrough Test. Units may be expressed as ug/ml.

Procedure for Milking the Cow

These are the generic steps to perform an elution of a dry column system. Currently the only two commercially available generators are based on the dry column.

Materials:

Gloves and lab coat

Generator with 2 needle seal vials

1 eluant* charge vial (10 cc of sterile non-pyrogenic normal saline (0.9%) in a vial)

1 eluate* collection vial (evacuated sterile non-pyrogenic collection vial)

1 eluting shield

3 70 % isopropyl alcohol wipes
Chemistry definitions:

Eluant is the solvent used in the process of elution.

Eluate is solvent which passes thru a column and removes the sample component from the stationary phase.

Elution Instruction:

1. Waterproof gloves should be worn during the elution.

2. Perform all subsequent operations aseptically.

3. Remove the needle seal vial from the eluant charge well and discard as radioactive waste (review Figure 5).

4. From a new eluant charge vial (cow udder) remove the flip-top cap and swab septum with bactericide (ie 70 % % isopropyl alcohol) and allow to dry.

5. Insert the eluant vial into the charge well (milking tips). Vial should be firmly inserted to assure puncture of septum.

6. Open base of elution shield (see Figure 6) and insert an eluate collection vial (milk tank) from which the flip-off seal has been removed. Screw base back on securely. Swab the exposed vial septum with a bactericide.

7. Remove the needle seal from the collect well and handle as radioactive.

8. Insert shielded eluate collection vial in collect well. Elution should commence within 30 seconds and can be visually checked by appearance of bubbles in the eluant charge vial.

9. To assure proper yield and functioning, elution must proceed to completion as evidenced by emptying of the charge vial. Allow generator to elute for at least 3 minutes after the charge has been drained.

10. After elution has been completed, remove as a unit the shielded collection vial.

11. Obtain the collection needle seal vial, and using a bactericide, swab the septum of the collection needle seal vial and insert over the collection needle. The eluant vial is sterile and should stay in place until the next elution, functioning as a seal for the needles within the charge well.

12. Proceed with the Molybdenum-99 breakthrough test below.
Molybdenum-99 Breakthrough Test

Materials:

Tongs
Generator eluate and shield (instructor may substitute Co-57 if Tc-99m not available)
Dose calibrator
Mo-99 assay kit (lead canister (Figure 7) and insertion holder)
Instructions:

1. Adjust the dose calibrator to assay Mo-99.

2. Place the empty lead canister into the dose calibrator and record the displayed background activity (BG) in uCi.

3. Using tongs transfer the generator eluate from the elution shield to the Mo assay canister and assay. This value will represent the Mo-99 (Mo) in uCi.

4. Remove Mo assay canister from well and readjust the dose calibrator for Tc-99m.

5. Remove eluate from Mo assay canister and place into dose calibrator well.

6. The Tc-99m activity of the eluate will then be measured without the canister at the Tc-99m calibration setting (Tc) in mCi.

7. The ratio of Mo-99 contamination will calculate as: \[ \frac{(\text{Mo-BG}) \times \text{CF}*}{\text{Tc}} \]

8. Retrieve eluate from well and place into shield.

9. The maximum allowable Mo-99 contamination should be no more than 0.15 microcuries of Mo-99 per millicurie of Tc-99m at the time of calibration or administration to the patient.

10. Label the collection vial as Tc-99m pertechnetate, indicating the activity, the date and the time.

* The procedure for measuring molybdenum concentration is based on the use of a molybdenum breakthrough “pig” or canister (Figure 7). The manufacturer will specify the Mo-99 correction factor to convert from measured Mo-99 to total Mo-99.
Aluminum Contamination Test

Materials:

Gloves and lab coat
Generator eluate and shield
TB syringe with needle
Test strips
Standard aluminum solution (10 ug/ml)

Instructions:

1. Using syringe withdraw a very small volume of the eluate.
2. Spot test strip with a microdrop from the syringe needle.
3. Place another very small drop from the standard aluminum solution on same strip.
4. Compare colors (shades of pink) of two drops. If the intensity of the generator eluate is less than the standard, the alumina contamination is less than 10 ug/ml and passes.
Questions:

1. Doses from a radiopharmacy usually expire in 12 hours. Discuss what happens with the ratio of Mo-99 to Tc-99m during that time.

2. If you were interested in injecting a large activity of Tc-99m in a small volume, perhaps for a dynamic nuclear medicine study, why would you prefer to have the pharmacy make a fresh elution of the generator?

3. How is “breakthrough” related to radionuclidic purity when talking about a Moly generator?

4. What purpose does the correction factor for the moly canister serve?

After you answer these questions turn in a copy of this page in for credit to the Physics and Education Offices.

Resident Name (print): ________________________________

Completed lab on: ___/___/______

Signature of individual supervising lab: ______________________