

AC 2007-620: DEVELOPMENT OF A RADIOCHEMISTRY LABORATORY FOR THE PRODUCTION OF TC-99M USING NEUTRON ACTIVATION

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DEVELOPMENT OF A RADIOCHEMISTRY LABORATORY FOR THE PRODUCTION OF ^{99m}Tc USING NEUTRON ACTIVATION

Abstract

Many health care professionals increasingly rely on the use of radiopharmaceuticals in diagnosis and therapy. ^{99m}Tc is the world's most widely used radioisotope in nuclear diagnostic imaging. A small amount of ^{99m}Tc is incorporated in a carrier molecule and injected into the patient's blood stream which is then used for imaging. Selective accumulation of the ^{99m}Tc in specifically targeted internal organs is achieved through the design of the carrier molecule. Traditionally it is produced from fission of uranium to produce ^{99}Mo which then decays to ^{99m}Tc . The goal of this work is to set up a comprehensive graduate radiochemistry laboratory to isolate ^{99m}Tc using the neutron activation of stable ammonium molybdenate. Included in the laboratory is an overview of the nuclear medicine information of ^{99m}Tc , the radiation dose received for specific medical diagnoses, and the construction of an efficiency curve for a germanium detector that can be used for activity measurements of other medical isotopes produced.

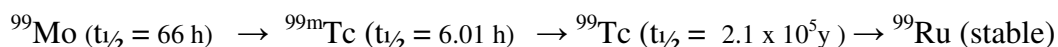
Introduction

At the University of Texas at Austin we are currently on our second three-year Radiochemistry Education Award Program (REAP) for graduate studies. For the first three years of REAP we developed several laboratories to augment the lecture portion. These included: 1. *Determination of Fission Activity*, 2. *Solvent Extraction of Selenium*, 3. *Alpha Analysis*, and 4. *Liquid Scintillation Lab*. For the second round of REAP we are committed to develop three laboratories: 1. *Production of ^{99m}Tc* , 2. *Compton Suppression Low Level Gamma-Ray Counting* and 3. *Solvent Extraction of Fission Products*. There continues to be great interest among engineers and chemists to enter the medical profession either as practicing doctors or researchers in oncology and other related areas. The development of a laboratory devoted to the understanding of isotope production, its pharmacology and application in diagnosis is well suited for training and education for graduate students in our REAP program. Here we present the first of our three planned laboratory experiments "The Development of a Radiochemistry Laboratory for the Production of ^{99m}Tc Using Neutron Activation".

This laboratory is based on the original work published in 2006 by Buckley *et al.*¹ named "Radioisotopes in Medicine: Preparing a Technetium-99m Generator and Determining Its Efficiency". A complete laboratory procedure for the preparation of ^{99m}Tc generator and determining its efficiency was also written and sent to the University of Texas. This laboratory was developed at the Washington State University and Oregon State University; both have TRIGA reactors similar to that at the University of Texas. The goal of the present work was to enhance the laboratory by having a more detailed description of the applications in medical imaging and pharmacology of ^{99m}Tc . As well, the radiation dosimetry considerations are also explained. To improve the learning experience for general production of radioisotopes in medicine we included the calibration of an efficiency curve for a germanium detector which would enable the students to deduce the total activity for any isotope produced. This is one aspect which was not included in the laboratory developed by Buckley *et al.*¹ Because ^{99}Mo is currently produced mainly from highly enriched uranium fission the IAEA completed up a Coordinated Research Project² on ways to produce molybdenum from neutron activation using "gel generators". A general history of technetium generators and additional information on their use is available from the Royal Society of Chemistry on the internet³.

^{99m}Tc and Metastable States

Typical lifetimes of nuclear excited states are on the order picoseconds or less. However, in some instances, the nuclear excited state can last considerably longer. This is because the transition to the lower energy state is quantum mechanically "forbidden". These relatively long-lasting excited states are called metastable states. In the case of a metastable state, the excited nucleus may emit gamma radiation to achieve a lower energy state. An example of a metastable state is ^{99m}Tc , where m denotes the metastable state. ^{99m}Tc decays by gamma emission to ^{99}Tc . When a metastable state relaxes to a lower energy state without a change in proton or mass number, it is termed an "internal transition". The complete decay sequence is shown below.



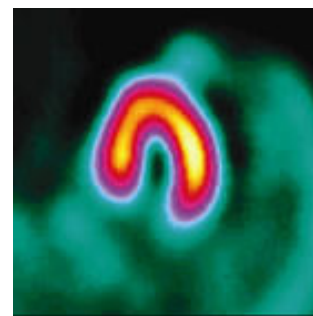
Medical Imaging

Many health care professionals increasingly rely on the use of radiopharmaceuticals in diagnosis. The world's most widely used radioisotope in nuclear diagnostic imaging is ^{99m}Tc . A small amount of ^{99m}Tc is incorporated in a carrier molecule and injected into the patient's blood stream. Selective accumulation of the ^{99m}Tc in specifically targeted internal organs is achieved through the design of the carrier molecule. ^{99m}Tc emits gamma radiation which allows for imaging of the organs with a gamma camera. Diagnostic images of the heart, brain, liver, kidneys, spleen, lungs, bones, and blood flow, among others, are produced in a non-invasive manner with relative ease. Its short half life, ease of incorporation into a variety of carrier molecules, low energy gamma emission, and rapid excretion make ^{99m}Tc ideal for obtaining images of the major organs of the human body.

When present in 0.9% sodium chloride, ^{99m}Tc is a sterile, non-pyrogenic, diagnostic radiopharmaceutical suitable for intravenous injection, oral administration, and direct instillation. The eluate is a clear liquid with a pH of 4.5-7.5. ^{99m}Tc decays by isomeric transition with a physical half-life of 6.02 hours. Because of ^{99m}Tc 's short half-life, hospitals receive irradiated ^{99}Mo with its half-life of 66 hours decays and use it as a generator to elute the ^{99m}Tc . The physical decay characteristics of ^{99}Mo are such that only 88.6% of the decaying atoms form ^{99m}Tc . This means that only 78% of the activity remains after 24 hours; 60% remains after 48 hours, etc. Since the ^{99}Mo is constantly decaying to fresh ^{99m}Tc , it is possible to elute the generator at any time. Although generator elutions may be made at any time, the amount of ^{99m}Tc available depends on the interval from the last elution. Approximately 47% of maximum ^{99m}Tc is reached after 6 hours and 95% after 24 hours as shown in Figure 1. A list of the medical applications for ^{99m}Tc is given below.

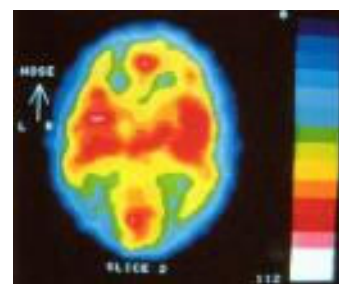
Sodium Pertechnetate ^{99m}Tc Injection is used in adults as an agent for:

- Brain Imaging (including cerebral radionuclide angiography)
- Thyroid Imaging
- Salivary Gland Imaging
- Placenta Localization
- Blood Pool Imaging (including radionuclide angiography)
- Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux.
- Nasolacrimal Drainage System Imaging



Sodium Pertechnetate ^{99m}Tc Injection is used in children as an agent for:

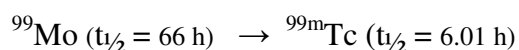
- Brain Imaging (including cerebral radionuclide angiography)
- Thyroid Imaging
- Blood Pool Imaging
- Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux.



Radiation risks associated with the use of sodium pertechnetate ^{99m}Tc injection are greater in children than in adults and, in general, the younger the child, the greater the risk owing to greater absorbed radiation doses and longer life-expectancy. These greater risks should be taken firmly into account in all benefit-risk assessments involving children.

Chemical Theory of a ^{99m}Tc Generator

Since the radiological half life of ^{99m}Tc is relatively short, its manufacture for commercial distribution is impractical. It is therefore produced in hospitals as needed through the use of ^{99m}Tc generators. Since the ^{99}Mo is constantly decaying to fresh ^{99m}Tc , it is possible to elute the generator at any time. These generators contain ^{99}Mo adsorbed onto a column of Al_2O_3 (aluminum oxide, or alumina). The ^{99}Mo undergoes radioactive decay to form ^{99m}Tc :



Eventually, a point is reached where the rate of formation of ^{99m}Tc equals its rate of decay. If the half-life of the parent radionuclide is approximately ten times the half life of the daughter product, this point is called “transient equilibrium”. Transient equilibrium is reached after four half-lives of the daughter product have passed. At this point, the ^{99m}Tc activity appears to decay with the half-life of ^{99}Mo . The ^{99m}Tc is collected as needed by passing a saline solution through the column, which selectively elutes the ^{99m}Tc , while the ^{99}Mo is retained on the column, where it continues to decay and produce more ^{99m}Tc . These systems are often referred to as “cows” that can be “milked” to generate ^{99m}Tc . Systems of this type are available commercially and are common in hospitals. The alumina oxide in the column is a polar solid. Here, an ammonium molybdate solution is used as a ^{99}Mo source, and is eluted with 0.9% sodium chloride. ^{99}Mo is also polar, and so it is embedded in the stationary phase, while the non-polar ^{99m}Tc acts as the mobile phase which passes through the column to be collected.

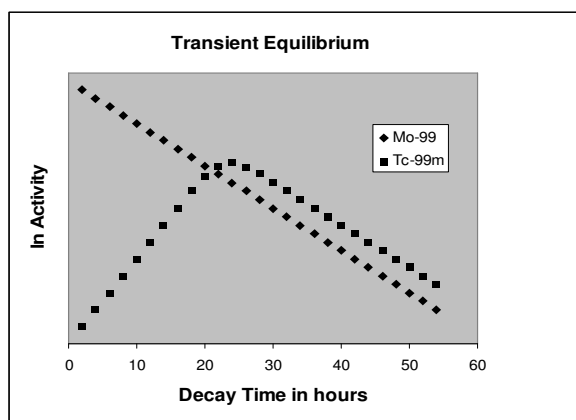


Figure 1. Transient equilibrium. Initially, the activity of the parent (^{99}Mo) is much greater than the activity of the daughter (^{99m}Tc). After approximately four half lives of ^{99m}Tc have passed, transient equilibrium is established, and the daughter appears to decay with the half-life of the parent.

Clinical Pharmacology

The pertechnetate ion distributes in the body similarly to the iodide ion but is not organified when trapped in the thyroid gland. Pertechnetate tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. It also concentrates in the choroid plexus, thyroid gland, salivary glands, and stomach. However, in contrast to the iodide ion, the pertechnetate ion is released unchanged from the thyroid gland.

After intravascular administration it remains in the circulatory system for sufficient time to permit blood pool, organ perfusion, and major vessel studies. It gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

Following the administration of sodium pertechnetate ^{99m}Tc injection as an eye drop, the drug mixes with tears within the conjunctival space. Within seconds to minutes it leaves the conjunctival space and escapes into the inferior meatus of the nose through the nasolacrimal drainage system. During this process the pertechnetate ion passes through the canaliculi, the lacrimal sac and the nasolacrimal duct. In the event of any anatomical or functional blockage of the drainage system there will be a backflow resulting in tearing (epiphora). Thus the pertechnetate escapes the conjunctival space in the tears.

While the major part of the pertechnetate escapes within a few minutes of normal drainage and tearing, it has been documented that there is some degree of transconjunctival absorption with a fractional turnover rate of 0.015/min in normal individuals, 0.021/min in patients without any sac, and 0.027/min in patients with inflamed conjunctiva due to chronic dacryocystitis. Individual values may vary but these rates are probably representative and indicate that the maximum possible pertechnetate absorbed will remain below one thousandth of that used in other routine diagnostic procedures.^{4,5}

Dosage and Administration

Each eluate of the ^{99m}Tc generator should not contain more than 0.0056 MBq (0.15 mCi) of ^{99}Mo per 37 MBq (1 mCi) of ^{99m}Tc per administered dose at the time of administration, and not more than 10 μg of aluminum per milliliter of the ^{99m}Tc Generator eluate, both of which must be determined by the medical professional before administration. Since the eluate does not contain an antimicrobial agent, it should not be used later than one working day after the elution.

Sodium Pertechnetate ^{99m}Tc injection is usually administered by intravascular injection but can be given orally. For imaging the urinary bladder and ureters (direct isotopic cystography), the Sodium Pertechnetate ^{99m}Tc Injection is administered by direct instillation aseptically into the bladder via a urethral catheter, following which the catheter is flushed with approximately 200 mL of sterile saline directly into the bladder. The dosage employed varies with each diagnostic procedure. If the oral route is elected, the patient should fast for at least six hours before and two hours after administration. When imaging the nasolacrimal drainage system, the sodium pertechnetate ^{99m}Tc Injection is instilled by the use of a device such as a micropipette or similar method which will ensure the accuracy of the dose.

The suggested dose range employed for various diagnostic indications in the average adult patient (70kg) is shown in Table 1.⁵

Table 1 Dose ranges for various diagnostics in average adults

Medical Use	MBq	mCi	μCi/kg body weight
Vesico-ureteral Imaging	18.5 - 37	0.5 - 1	-
Brain Imaging	370 - 740	10 - 20	140 to 280
Thyroid Gland Imaging	37 - 370	10 - 20	60 to 80
Salivary Gland Imaging	37 - 185	1 - 5	140 to 280

The recommended dosage range in average pediatric patient is shown in Table 2.⁵

Table 2 Dose ranges for various diagnostics in average pediatric patients

Medical Use	MBq	mCi	μCi/kg body weight
Vesico-ureteral Imaging	18.5 - 37	0.5 - 1	-
Brain Imaging	5.18 - 10.36	0.14 - 0.28	140 - 280
Thyroid Gland Imaging	2.22 - 2.96	0.06 - 0.08	60 - 80
Blood Pool Imaging	5.18 - 10.36	0.14 - 0.28	140 - 280

A minimum dose of 111 to 185 MBq (3 to 5 mCi) should be employed if radionuclide Angiography is performed as part of the blood pool or brain imaging procedure.

Up to one gram of pharmaceutical grade potassium perchlorate in a suitable base or capsule may be given prior to administration of sodium pertechnetate ^{99m}Tc injection. When sodium pertechnetate ^{99m}Tc injection is used in children for brain or blood pool imaging, the administration of potassium perchlorate is especially important in order to minimize the absorbed radiation dose to the thyroid gland. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration of the dose. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The solution to be administered as the patient dose should be clear and contain no particulate matter.

Radiation Dosimetry

The estimated absorbed radiation doses to an average adult patient (70 kg) from an intravenous injection of a maximum dose of 1110 MBq (30 mCi) of sodium pertechnetate ^{99m}Tc injection distributed uniformly in the total body of subjects not pre-treated with blocking agents such as pharmaceutical grade potassium perchlorate are shown in Table 3. For placenta localization studies, when a maximum of 111 MBq (3 mCi) is used, it is assumed to be uniformly equilibrated between maternal and fetal tissues.

Table 3 Absorbed Radiation Doses (Adults) of 1110 MBq⁵

Tissue	Resting Population	Active Population	mGy/111MB (rads/3mCi)
Bladder Wall	15.9 (1.59)	25.5 (2.55)	-
Gastrointestinal Tract:			
Stomach Wall	75.0 (7.50)	15.3 (1.53)	-
Upper Large Intestine Wall	20.4 (2.04)	36.0 (3.60)	-
Lower Large Intestine Wall	18.3 (1.83)	33.0 (3.30)	-
Red Marrow	5.7 (0.57)	5.1 (0.51)	-
Testes	2.7 (0.27)	2.7 (0.27)	-
Ovaries	6.6 (0.66)	9.0 (0.90)	-
Thyroid	39.0 (3.90)	39.0 (3.90)	-
Brain	4.2 (0.42)	3.6 (0.36)	-
Whole-Body	4.2 (0.42)	3.3 (0.33)	-
Placenta	-	-	0.5 (0.05)
Fetus	-	-	0.5 (0.05)

In pediatric patients, the maximum radiation doses of 185 MBq (5 mCi) of sodium pertechnetate ^{99m}Tc injection administered to a neonate (3.5 kg) for brain or blood pool imaging with radionuclide angiography are shown in Table 4. In pediatric patients, an average 30 minute exposure to 37 MBq (1 mCi) of sodium pertechnetate ^{99m}Tc injection following instillation for direct cystography, results in an estimated absorbed radiation dose of approximately 0.30 mGy (30 millirads) to the bladder wall and 0.04 to 0.05 mGy (4 to 5 millirads) to the gonads.

Table 4 Absorbed Radiation Doses (Pediatric)⁵

Tissue	mGy/37MBq (rads/1mCi)	mGy/185MBq (rads/5mCi)
Thyroid (without perchlorate)	46	230
Thyroid (with perchlorate)	9.7	48.5
Large Bowel (with perchlorate)	19	95.5
Testes	1	5.1
Ovaries	2.2	11
While-Body	1.5	7.6

Diagnosis of tear ducts also use sodium pertechnetate ^{99m}Tc injection. The absorbed dose for patients undergoing dacryoscintigraphy is shown in Table 5.⁵

Table 5 Absorbed Radiation Dose from Dacryoscintigraphy

Target Organ	Absorbed Dose mGy/3.7MBq	Absorbed Dose (mrad/100μCi)
Eye Lens:		
If lacrimal fluid turnover is 16%/min	0.14	14
If lacrimal fluid turnover is 100%/min	0.022	2.2
If drainage system is blocked	4.02	402
Total Body*	0.011	1.1
Ovaries*	0.03	3
Testes*	0.009	0.9
Thyroid*	0.13	13

Activity

In this experiment, the activity of ^{99m}Tc at any time after irradiation can be calculated by the approximate equation:

$$A_d = [\lambda_d (\lambda_d - \lambda_p)^{-1}] [A_p^0 e^{-\lambda_p t}]$$

where:

A_d = activity of the daughter

λ = decay constant for the parent or daughter, $\ln 2 / t_{1/2}$

A_p^0 = activity of the parent at $t = 0$ (upon completion of irradiation)

t = time since completion of irradiation

The maximum ^{99m}Tc activity is given by: $T_{\max} = (\lambda_d - \lambda_p)^{-1} \ln(\lambda_d/\lambda_p)$

The amount of ^{99}Mo (in mCi) produced from 5.0 mg ammonium molybdate ($(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$) irradiated for 1 hour at $6 \times 10^{12} \text{ cm}^{-2} \text{ s}^{-1}$ is given by:

$$A = N\sigma\phi (1 - e^{-\lambda t})$$

where:

A = activity of ^{99}Mo in Becquerels at the end of irradiation

N = number of ^{98}Mo atoms

σ = thermal Neutron capture cross section for ^{98}Mo in cm^2

ϕ = thermal Neutron flux in the reactor in $\text{cm}^2 \text{ s}^{-1}$

λ = decay constant for ^{99}Mo in h^{-1}

t = irradiation time in h

There the total activity is calculated to be 0.91 μCi .

Vacuum Filtration Results and Procedure

When the experiment was performed at the University of Texas at Austin, a vacuum filtration system was used to elute the ^{99m}Tc through the activated alumina. Our results found no peak at 181 KeV suggesting that the upper limit of the background interference was above the ^{99m}Tc peak. To avoid this problem, either a higher activation or larger sample of ^{99}Mo is needed for a larger amount of ^{99m}Tc to be filtrated out.

We used a vacuum filtration system to significantly decrease the time needed to elute the ^{99m}Tc from the activated alumina. The required 20 mL can be eluted through the column in less than five minutes when vacuum filtrated. To set up the vacuum filtration system, slide the column containing activated alumina into a rubber stopper and secure the rubber stopper in a vacuum filtration Erlenmeyer flask. These look like regular Erlenmeyer flasks, but with an arm extending outwards near the neck of the flask. Secure the flask in place with metal clamps and attach one end of a rubber piping hose to the arm of the Erlenmeyer. The other end of the rubber hose should be attached to the vacuum system outlet on the outside of the fume hood near the gas and water outlets. Before you perform the vacuum filtration procedure, double check to make sure the flask is secure, turn on the vacuum, and slowly pour the irradiated Molybdenum solution into the top of the column. **CAREFUL: IF Poured TOO QUICKLY THE ALUMINA AND ^{98}Mo SOLUTION WILL SPLASH OUT OF THE COLUMN!** Continue to pour until all 20 mL of solution has been filtrated through the column. Collect a sample of filtrated solution with a vial labeled “sample” and a sample of ^{99}Mo solution that has not been filtrated with a vial labeled “standard”.

Calculate the ⁹⁹Mo breakthrough in terms of activity:

The federally allowed limit for the amount of ⁹⁹Mo activity present in the ^{99m}Tc that is injected into a patient is 0.15 microcuries of Mo per millicuries of ^{99m}Tc. The mCi of ^{99m}Tc obtained in is calculated using the following equation:

$$\frac{P(140)}{0.89 (3.7 \times 10^7) (t)}$$

where P(140) is the number of net counts for the ^{99m}Tc peak at 140 keV. Divide the counts by the number of seconds that the sample was counted for in order to get counts per second. ^{99m}Tc atoms only emit gamma radiation of 140 keV 89% of the time. Therefore, one must adjust the peak counts for ^{99m}Tc by this *branching ratio*. In order to convert the number of counts per second to the units of mCi, divide by the factor of 3.7 x 10⁷ decays per second/mCi. The μCi of ⁹⁹Mo is determined by using the number of counts per second for the ⁹⁹Mo peak at 181 keV, a branching ratio of 0.0599, and the constant 3.7 x 10⁴ disintegrations per second/μCi. Now one can calculate the ratio of μCi ⁹⁹Mo/mCi ^{99m}Tc. As stated in Buckely *et al.*¹ the detector efficiency at 140 keV and 181 keV are similar and thus there is no need that this be taken into account. However, in our laboratory we decided to add procedure to actually construct an efficiency curve from a calibrated ¹⁵²Eu source. We found this procedure to be pedagogically important in case activities of other isotopes were ever needed. Below is the standard XCEL spread sheet used for deduce an efficiency curve,

Table 6 Calculation of a germanium detector efficiency curve

Half-life of ¹⁵²Eu	13.542	Y
	427353019.2	s
Decay Constant (lamda)	1.62195E-09	1/s
Activity	106.39	kBq
	106390	Bq
Certification Date	1/1/1999	0:00
Current Date	6/10/2003	15:00
Decay Time	1621.63	days
	140108400.00	seconds
Current Activity	84763.25443	Bq

Highlight the B9 cell. Click on equal sign. Type B8 minus B7. Then format B9 by right clicking and selecting format cells. Select the Number tab, chose number from the category menu, and click OK. Convert days to seconds by multiplying by 24 and 3600.

found by **A = Aoe^-((lamda)(decay time))**

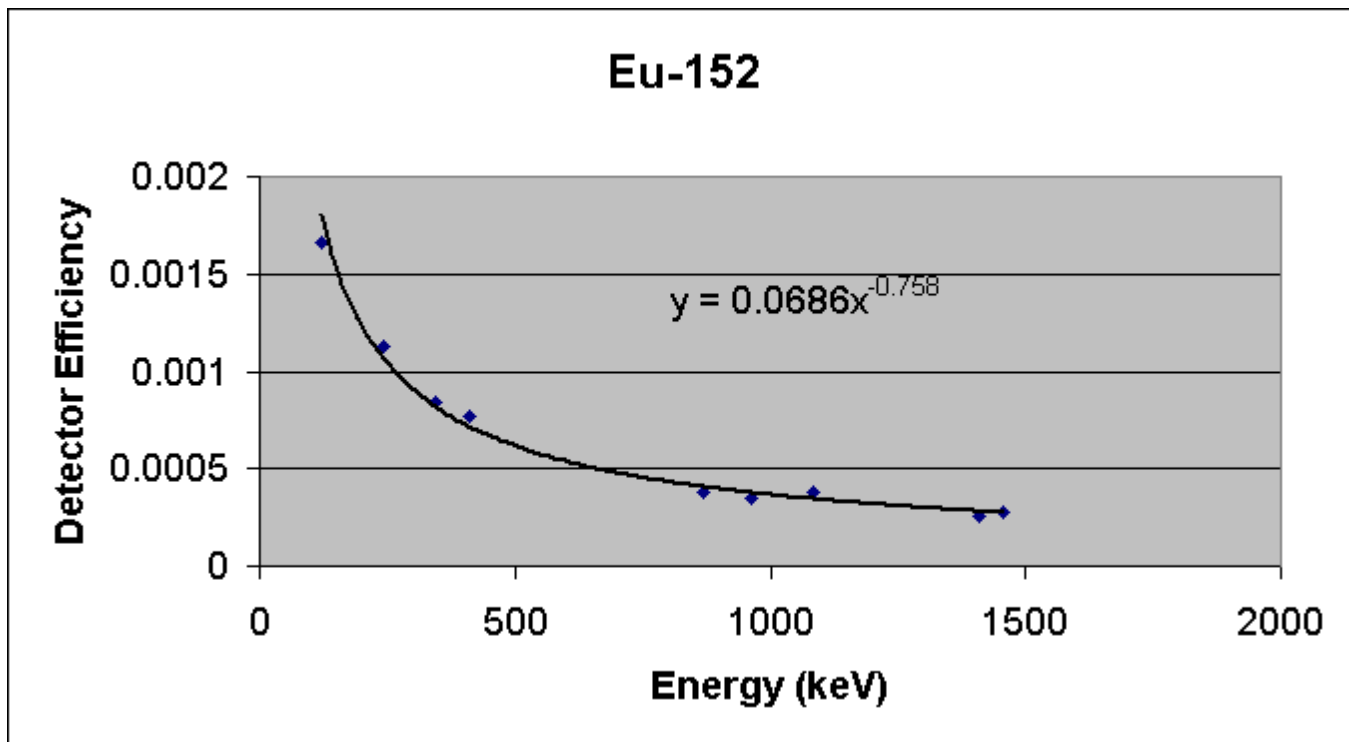
Count time (real)	71272.06	s
Count time (live)	71178.03	s

Counts Counts equal the net area counts given by the collection program
Gammas Gammas equal current activity times time counted times intensity over 100
Efficiency Efficiency equals the number of Counts over the number of Gammas

Plot

Click on an empty cell in an empty column. Click on the insert menu and select chart. Select XY scatter from the chart type menu and click next. Click on the series tab and then click on the add button. Click on the button on the right of the X values field. Highlight the energies in column A and press enter. Click on the button on the right side of the Y values field. Highlight the efficiencies in column H and press enter and then press next. Type in the appropriate x-axis heading, y-axis heading, and chart title. Click on next and then click on finish. Right click on any data point in the graph. Select Add Trendline. Select the Power regression type. Click on the Options tab. Put a check in the "Display Equation on Chart" checkbox and then click OK.

Energy	Intensity	Counts	Gammas	Efficiency
121.8	28.67	2.88E+06	1.73E+09	0.001665
244.7	7.61	5.18E+05	4.59E+08	0.001127
344.3	26.6	1.34E+06	1.6E+09	0.000837
411.1	2.233	1.03E+05	1.35E+08	0.000767
867.4	4.2	9.68E+04	2.53E+08	0.000382
964.1	14.6	3.11E+05	8.81E+08	0.000353
1085.9	9.9	2.28E+05	5.97E+08	0.000382
1408.0	20.8	3.28E+05	1.25E+09	0.000261



Conclusions

We have taken a laboratory procedure devised by Buckley *et al.*¹ and have added features detailed information of ^{99m}Tc for medical imaging, pharmacology and radiation dosimetry. As well, we added an experimental section for germanium detector efficiency calibration to be able to deduce the activity of any medical isotope used at any energy. This laboratory has now been integrated into the graduate course with the other experiments.

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