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RESEARCH ESTABLISHMENT
LUCAS HEIGHTS

TECHNETIUM-99m GENERATORS PREPARED FROM FISSION PRODUCED MOLYBDENUM-99 - QUALITY CONTROL AND PERFORMANCE ASPECTS

by

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ABSTRACT

^{99m}Tc generators distributed by the A.A.E.C. are based on ^{99}Mo extracted from irradiated uranium.

The production of these generators and the methods employed in their testing are described.

The quantity of ^{99m}Tc eluted from these generators varied with pH of the eluant with maxima at pH 0.5 - 0.9, 3, 4.7 - 6.7 and > 9.5. Terminal autoclaving reduced the yield by 10 - 20 per cent.

continued ...

ABSTRACT (continued)

An ionisation chamber method and a γ-spectrometry method were developed to measure the radionuclidic purity of eluates. Impurity levels were lower than the minimum permitted concentrations set by the USAEC. The major impurities, ^{99}Mo, ^{132}I and ^{103}Ru can be reduced to insignificant levels by discarding the first few ml of eluate at each elution.

Soluble aluminium concentration in the eluate decreased exponentially with eluant volume. In most cases it was less than 5 μg/ml after 100 ml had been passed through the generator.

Stringent quality control procedures ensured a sterile and pyrogen free product.

The results of this study confirm the value of the fission based ^{99m}Tc generator and remove any existing obstacles to its wider exploitation.

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AGE; EFFICIENCY; ELUTION; GAMMA SPECTROMETERS; IMPURITIES; IONIZATION CHAMBERS; MOLYBDENUM 99; NUCLIDES; PERFORMANCE; pH VALUE; PRESSURE; PRODUCTION; TECHNETIUM 99; TEMPERATURE.

CONTENTS

1. INTRODUCTION

The use of ^{99m}Tc chromatographic generators prepared from fission produced ^{99}Mo has declined in recent years. Those prepared from irradiated ^{98}Mo are preferred, presumably owing to the practical difficulties associated with the processing of irradiated uranium and the risk of radionuclidic impurities appearing in the separated ^{99m}Tc.

However, although the processing of irradiated uranium and associated fission products requires elaborate equipment, a small volume fission based generator containing carrier free ^{99}Mo has certain technical and economic advantages. For example, if the generator producer has no domestic supply of enriched ^{98}Mo and no nuclear reactor with very high flux irradiation facilities ($> 10^{14}$n cm^{-2} sec^{-1}) then high activity generator production from irradiated ^{98}Mo is uncertain, expensive and rather inefficient. Hence, provided that the problems of radionuclidic impurities can be overcome, there is a case for the development and refinement of fission produced ^{99}Mo generators.

This paper describes the production of fission based generators, the methods used to control and measure quality and performance, and examines the radiological consequences of the very low levels of radionuclidic impurities in the eluted fractions of ^{99m}Tc.

2. PRODUCTION OF FISSION BASED GENERATORS

Irradiated uranium dioxide pellets are dissolved in 8 molar nitric acid at 90°C; the solution is purged continuously with nitrogen to remove the liberated ^{133}Xe and ^{131}I. When dissolution is complete the solution is diluted with water to an acid concentration of 1 molar and passed down an alumina column where the ^{99}Mo and ^{132}Te are absorbed. The alumina column is washed with 1 molar nitric acid, water and finally 0.01 molar ammonium hydroxide to remove all the unabsorbed fission products. The column is then eluted with 1 molar ammonium hydroxide to separate the ^{99}Mo. The eluate is filtered* and potassium iodide, potassium iodate and concentrated nitric acid are added and the solution is boiled.

During boiling the iodine produced by the reaction

$$5I^- + IO_3^- + 6H^+ \longrightarrow 3I_2 + 3H_2O$$

distils out of the acid solution. The radioiodines are completely removed only

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* $^{132}Te/^{132}I$ contamination arose from a breakthrough of alumina in the ammoniacal eluate. Filtering this solution before making it acid with HNO_3 reduces the ^{132}I content of subsequent generator eluates to a non-detectable level.

if the acid solution is evaporated to dryness and the residue baked for about 10 minutes. During baking ammonium nitrate, produced by neutralising the ammoniacal eluate with nitric acid, sublimes.

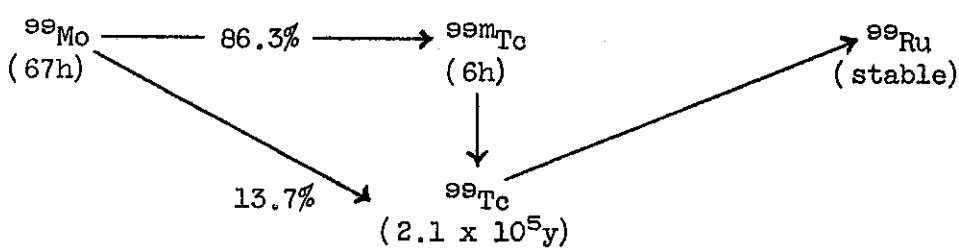
When cool, the residue is treated with warm 1 molar nitric acid to re-dissolve the molybdate (^{99}Mo). The solution is filtered to remove any insoluble material and finally sampled for radioactive content and radionuclidic purity.

The solution is then transferred to the loading apparatus and injected into the small generator vials. After the required volume of the ^{99}Mo stock solution has passed through the vial, it is washed with isotonic sodium nitrate solution and then immediately measured for radioactivity in an ionisation chamber as separated ^{99}Mo (i.e. free from daughter ^{99m}Tc). Finally the generator is autoclaved at 121°C for 33 minutes.

In the quality control tests described below the ^{99m}Tc was separated from the generator as pertechnate by passing a gravity drip feed of normal saline. The usual procedure was to collect and agitate the first 25 ml of eluate, but for some investigations the first 6 ml was separated. On a few occasions the eluate was collected as 25 separate 1 ml fractions.

3. GENERATOR PERFORMANCE - MILKING EFFICIENCY

As a source of ^{99m}Tc the generator has certain output limitations, and for successful application in nuclear medicine these must be known. The growth, and hence availability, of ^{99m}Tc is governed by the decay scheme for ^{99}Mo:



in which, after some time ^{99}Mo and ^{99m}Tc will be in equilibrium.

It is possible to calculate the activity of ^{99m}Tc present in a ^{99}Mo: ^{99m}Tc system, given the ^{99}Mo activity and the time, T, since the previous separation. The ^{99}Mo activity is expressed by

$$A_1 = A^o e^{-\lambda_1 T}$$

and the ^{99m}Tc activity by

$$A_2 = \frac{0.863\ \lambda_2}{\lambda_2 - \lambda_1} A^o (e^{-\lambda_1 T} - e^{-\lambda_2 T})$$

where the subscript 2 refers to ^{99m}Tc and 1 refers to ^{99}Mo,

A = activity at time T

A^O = initial activity of ^{99}Mo

λ = decay constant.

Hence

$$\frac{A_2}{A_1} = \frac{0.863\ \lambda_2}{\lambda_2 - \lambda_1}\left(1 - e^{-(\lambda_2 - \lambda_1)T}\right)$$

Figure 1 shows the form of this expression. For example, a generator containing 100 mCi of ^{99}Mo, which has not been eluted for 20 hours should, in theory, yield 83.23 mCi of ^{99m}Tc on elution.

In practice the ^{99m}Tc obtained by elution is less than the calculated theoretical value. The ratio of the actual to theoretical value expressed as a percentage is called "milking efficiency". We investigated variations in milking efficiency with age and activity of the generator, autoclaving before and after loading and pH of eluant.

3.1 Effect of Age

Five autoclaved generators were eluted with normal saline (pH 5.5) over a period of eight days with little variation in milking efficiency as shown by results in Table 1.

TABLE 1

THE EFFECT OF AGE ON MILKING EFFICIENCY

Generator	Milking Efficiency (per cent)						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Mean
1	82.3	84.9	86.0	81.2	80.7	80.6	82.6 ± 2.7
2	78.4	81.9	83.2	82.4	89.8	82.7	83.1 ± 2.2
3	76.7	83.0	87.3	86.6	86.0	79.0	83.1 ± 3.7
4	80.0	82.8	88.0	-	-	80.3	82.8 ± 2.4
5	82.0	84.3	81.4	-	-	81.8	82.4 ± 1.0
Mean	79.9 ± 2.4	83.4 ± 1.2	85.4 ± 2.8	83.4 ± 2.8	85.5 ± 4.6	80.9 ± 1.4	

3.2 Effect of Initial Activity and Terminal Autoclaving

Generators with increasing initial activities were eluted on six consecutive days and the average milking efficiency measured. Terminal autoclaving was carried out for 7 generators. The results are shown in Table 2.

TABLE 2

THE EFFECT OF ACTIVITY AND TERMINAL AUTOCLAVING ON MILKING EFFICIENCY

Generator activity (initial) mCi ^{99}Mo	Terminal Autoclaving	Mean Milking Efficiency (per cent)
24	NO	92 ± 2
30	YES	67 ± 2
31	YES	69 ± 10
62	NO	95 ± 3
85	NO	94 ± 3
100	YES	82 ± 1
130	YES	82 ± 2
190	NO	90 ± 5
320	NO	90 ± 5
400	YES	83 ± 5
410	YES	82 ± 2
500	YES	83 ± 2

Initial activity had no effect, but the terminally autoclaved generators showed lower milking efficiencies. It was found that autoclaving of the generator bed prior to loading with the ^{99}Mo solution resulted in milking efficiencies similar to those of the non-autoclaved variety. Hence the difference in performance between autoclaved and non-autoclaved generators was not due to any change in the chemical affinity of the alumina towards ^{99m}Tc-pertechnetate which could slow down the rate of elution. It is more likely that the autoclaving process reduced the amount of ^{99}Mo molybdate available for the rapid separation which occurs with the passage of saline. This effect can be explained by a thermally induced diffusion of the absorbed molybdate into the centre of the alumina particles or the formation of an alumino-polymolybdate complex structure which prevents easy release of the pertechnetate ion.

3.3 Effect of Eluant pH

A series of eluants with various pH values was made by adding small quantities of either hydrochloric acid or sodium hydroxide to normal saline. These solutions were used to elute, daily, a range of non-autoclaved generators over a period of one week. The effect of eluant pH is shown in Table 3.

TABLE 3

THE EFFECT OF ELUANT pH ON MILKING EFFICIENCY

Eluant pH	Milking Efficiency (per cent)						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Mean
0.5	-	97.9	88.7	98.5	98.3	-	95.9 ± 2.6
0.9	96.0	100	100	100	100	-	99.2 + 0.8 - 2.0
1.4	-	43.7	23.5	14.2	-	15.0	24.1 ± 12.7
1.9	7.7	15.5	7.2	11.8	9.2	-	10.3 ± 3.0
2.5	35.7	28.5	53.5	21.4	25.4	-	32.9 ± 5.3
3.5	28.3	40.2	13.9	24.2	-	34.7	28.3 ± 9.0
4.3	0.9	0.2	2.6	0.5	3.5	3.7	1.9 ± 1.6
4.5	14.7	12.4	9.9	7.2	17.3	24.3	14.3 ± 5.7
4.7	76.0	100	93.0	94.2	88.2	85.8	89.5 ± 7.9
5.0	85.5	100	97.3	93.6	96.0	88.2	93.4 ± 5.4
5.5	94.0	100	97.3	86.4	96.1	-	94.8 ± 3.7
5.9	88.0	99.0	96.0	96.0	94.4	100	95.6 ± 3.0
6.4	95.0	100	97.0	95.0	88.8	87.2	93.8 ± 5.1
6.7	81.5	96.4	94.4	85.3	87.7	84.0	88.2 ± 5.7
7.4	-	4.1	7.2	8.1	3.6	1.8	5.0 ± 2.2
8.3	0.9	0.7	2.8	0.3	3.2	6.9	2.5 ± 2.2
8.5	13.2	16.5	14.2	14.1	16.1	18.8	15.5 ± 1.7
9.5	83.7	70.3	72.7	82.4	85.5	86.6	80.2 ± 6.4

The maxima at pH 0.5 - 0.9 pH 3, pH 4.7 - 6.7 and pH > 9.5 are difficult to explain because alumina has a strong buffering action which results in a constant eluate pH value of 4.5 using eluants with pH ranging from 3 to 10. However, elution of a generator with saline, pH 4.5, gave rise to a very poor milking efficiency (~ 15%). This indicates that the separation process is

very complex and may involve more than one step.

Chromatographic analysis failed to identify the presence of non pertechnetate species in the low yield eluates. It was concluded that the reduction in milking efficiency at certain pH values followed reactions which led to the formation of a strongly absorbed technetium species. These reactions could be reversed if the non-separating eluant was followed by saline at pH 5.5.

4. RADIONUCLIDIC PURITY

For the fission based ^{99}Mo: ^{99m}Tc system the presence of fission products other than ^{99}Mo has presented major problems in the past. ^{132}I (produced from ^{132}Te absorbed on the generator bed), ^{99}Mo (caused mainly by breakthrough of alumina) and ^{103}Ru are the main impurities (0.001 to 0.1 per cent of the total activity) with minor contributions from ^{131}I and ^{140}La (0.00001 to 0.001 per cent of the total activity). Two methods were used to determine the contribution of impurities. As they yield essentially the same result, the choice of method depends on the equipment available to the producer or user.

4.1 Activity Measurements

4.1.1 Ionisation chamber method

The method described by Richards and O'Brien (1969) was designed for generators produced from irradiated ^{98}Mo, where the only impurity is ^{99}Mo. It gives an erroneously high value for the total γ-impurities when applied to fission based generators. This is due to ^{132}I and ^{103}Ru emitting more energetic and/or abundant radiations than ^{99}Mo. The modified method depends on the interpretation of the responses of an ionisation chamber to the sample containing ^{99m}Tc, firstly unshielded then shielded in a lead container, at various times after elution.

(a) Apparatus and calibration

For these experiments a Nuclear Chicago, Mediac Dose Calibrator with direct digital read-out was used. All activity measurements were performed on the precalibrated ^{99m}Tc range and the results were recorded as microcuries ^{99m}Tc equivalent. The lead screen used was a cylindrical pot of nominal wall thickness 4 mm. The thickness of the lead screen need not be known exactly but the attenuation of the various gamma rays by the lead screen must be accurately known and is best determined experimentally. Radionuclidically pure ^{99m}Tc (specially prepared by multiple solvent extraction) was measured in the ionisation chamber, with and without the lead screen. The attenuation factor was found to be 780.

Pre-calibrated samples of ^{99}Mo (free from ^{99m}Tc), ^{132}I and ^{103}Ru were inserted into the lead pot to measure the response of the ionisation chamber

on the ^{99m}Tc range. The response factors for the lead pot used in our measurements were:

1 μCi ^{99}Mo = 0.455 μCi ^{99m}Tc equivalent
1 μCi ^{132}I = 9.7 μCi ^{99m}Tc equivalent
1 μCi ^{103}Ru = 1.69 μCi ^{99m}Tc equivalent.

(b) Measurement procedure

(i) Immediately after elution, agitate the eluate and transfer a sample to a 10 ml glass vial, dilute to 10 ml volume, cap and seal. Measure the total activity (unscreened) in the ionisation chamber (A μCi ^{99m}Tc equivalent).

(ii) Insert the sample into the lead pot and re-measure the ionisation chamber response (B μCi ^{99m}Tc equivalent).

(iii) Remove the sample from the lead pot and determine background (F_1 μCi ^{99m}Tc equivalent).

(iv) 24 hours after the first measurement, measure the ionisation chamber response to the screened sample (D μCi ^{99m}Tc equivalent).

(v) Remove the sample from the lead pot and determine the background response (F_2 μCi ^{99m}Tc equivalent).

(vi) 7 days after the first measurement, measure ionisation chamber response to the screened sample (E μCi ^{99m}Tc equivalent).

(vii) Remove the sample from the lead pot and determine the background (F_3 μCi ^{99m}Tc equivalent).

Since it is known that the impurity level in the eluted ^{99m}Tc solution is less than 1 per cent it is assumed that the ionisation chamber result, Aμci ^{99m}Tc, represents the total ^{99m}Tc present in the sample. The response of the ionisation chamber to the lead screened sample is the summed effect of the excited Pb X-rays, the greatly attenuated 140 keV photons of ^{99m}Tc, the partially reduced emissions of the more energetic contaminants, and the background radiation. That is,

$$I_{Total}\ (B\mu Ci) = I_{PbX} + I_{Tc} + I_{Mo} + I_{I} + I_{Ru} + I_{Bkgd}$$

where I = ionisation chamber response.

The value of $(I_{PbX} + I_{Tc})$ per μCi ^{99m}Tc is a characteristic of the lead screen used and the values of I_{Mo}, I_{I} and I_{Ru} can be deduced from the measurements taken at the different times.

Assuming that the only change in the quantity of impurities after 24 hours is due to the complete decay of the ^{132}I component, (this assumption is valid for ^{103}Ru but involves a 12 per cent error for ^{99}Mo) and using the experimentally determined value (780) of the attenuation factor for ^{99m}Tc radiations, then;

$$\text{per cent } ^{132}I = \frac{\left(B - \frac{A}{780} - F_1\right) - \left(D - \frac{A}{12,500} - F_2\right)}{0.097\ A}$$

$$\text{per cent } ^{99}Mo = \left[3.76\left(D - \frac{A}{12,500} - F_2\right) - 4.17\ (E - F_3)\right]\frac{100}{A} \quad ,$$

and $$\text{per cent } ^{103}Ru = \left[0.892\ (E - F_3) - 0.199\left(D - \frac{A}{12,500} - F_2\right)\right]\frac{100}{A} \quad .$$

4.1.2 Gamma spectrometry method

Gamma spectrometry appeared to be an obvious choice for the determination of the radionuclidic purity of ^{99m}Tc eluted from a fission based generator. However, direct spectral analysis of the low level impurities was impossible because of the overwhelming contribution of ^{99m}Tc. These difficulties were overcome by screening the sample with sufficient lead during counting to suppress the ^{99m}Tc contribution without drastically affecting that of the impurities. Figure 2 shows the spectral response for a typical sample with and without the lead screen.

A similar but rather more qualitative method has been described by Vesely and Cifka (1970). We have developed a quantitative method for determining the radionuclide impurities using a computer program to process the results of spectral analysis.

(a) Apparatus and calibration

The detector system consisted of a lithium drifted germanium (Ge (Li)) solid state detector coupled to a 512 channel pulse height analyser (Nuclear Data ND120). The detector was calibrated for efficiency using the standardised point sources ^{241}Am, ^{57}Co, ^{51}Cr, ^{137}Cs, ^{60}Co, ^{22}Na, ^{207}Bi, ^{54}Mn and ^{65}Zn. The results are shown in Figure 3. The dashed line is given by the empirically derived formula

$$\text{Efficiency} = 1.12 \times 10^{-4}\ EN^{-1.95} \quad ,$$

where EN is the photon energy in MeV. In the experimental situation, the efficiencies determined from the above equation were reduced by a factor of 0.44 because of differences in sample geometry.

The effective wall thickness of the lead pot enclosing the 10 ml sample vial was determined experimentally. The attenuation factor for the 0.140 MeV photons from ^{99m}Tc was found to be 8.4×10^4, giving an effective wall thickness of 4.0 mm.

The sample, sealed in a 10 ml vial and enclosed in the lead pot, was placed directly on the detector and, with the gamma spectrometer amplifier gain set for 5 keV per channel, counted for at least 100 minutes. The accumulated data were printed out in digital form and then transcribed to punched cards for computer analysis.

(b) Analysis and errors

A FORTRAN program, IMPURE, was used to calculate the ^{99m}Tc activity and the activities of the significant impurities, from the counts accumulated in selected photopeaks. Wherever possible a photopeak unique to the radionuclide under analysis was used, where overlapping occurred, peak integrals were corrected.

The activity of ^{99}Mo was determined first from its 0.74 MeV peak. The exact position of this peak was determined by a simple search routine. The counts in this channel and in the three channels on each side were summed. The counts due to background at this energy were assessed as the mean of the counts in the extremes of the seven channels summed. The total background, (mean value multiplied by seven), was subtracted from the total counts under the ^{99}Mo peak to give the net integral of the ^{99}Mo peak. If a calculated peak integral was negative (due to statistical fluctuations) its value was arbitrarily set to zero. The statistical significance of the peak integral, N, was also determined and was expressed as a standard deviation, $\sqrt{N}/N \times 100\%$.

To calculate the activity of ^{99}Mo, the peak total was corrected for lead screen attenuation, detector efficiency and photon yield per disintegration. A correction was also applied for decay during counting using the formula

$$C_o = \frac{\lambda N}{(1 - e^{-\lambda CT})}$$

where C_o = count rate at commencement of counting
CT = counting time
N = total counts for time CT
λ = decay constant.

The activity at the time of elution was calculated from the corrected count rate.

Since ^{99}Mo also has emissions of 0.37 MeV and 0.14 MeV which overlap the

photopeaks of ^{131}I and ^{99m}Tc, the program calculated and subtracted the ^{99}Mo contribution to these photopeaks at the appropriate stage. The activities of the other radionuclides were calculated in the sequence ^{99m}Tc, ^{140}La, ^{132}I, ^{131}I and ^{103}Ru in a similar fashion. The ^{103}Ru calculation included a correction for the contribution of ^{140}La to the 0.498 MeV peak. The calculations were simplified by nominating the channels for summation instead of searching as was done for ^{99}Mo.

The activity of each radionuclide was expressed as a percentage of the total activity. The activity percentage and standard deviation for each radionuclide were printed out. The channel in which the 0.74 MeV peak of ^{99}Mo occurs was also given and used to check the calibration of the spectrometer.

The accuracy of the gamma spectrometer method depends on several factors. The usual counting time is 100 minutes; a 10 mCi sample of ^{99m}Tc containing 0.3 μCi ^{99}Mo can be counted with a ± 5 per cent accuracy in this time. Longer counting times would be necessary to maintain this accuracy for very much lower contamination levels. The improved result does not justify the inconvenience of very long counting periods. The method of integrating the peak counts and the estimation of the attenuation factor, detector efficiency and geometrical correction factor, each involve an error of approximately ± 10 per cent. The total error, taken as the square root of the sum of the squares of the individual errors is approximately ± 20 per cent at the confidence level of 90 per cent.

The method has limitations. Firstly the sample must be counted within eight hours of elution to determine correctly the level of ^{132}I impurity. Secondly the impurity content must be less than 2 per cent of the total activity content. This should be the case with a correctly eluted generator. The results which indicate the second limitation were obtained from ^{99m}Tc samples intentionally adulterated with extraneous ^{99}Mo. These high levels of impurity result in an underestimate of the ^{99m}Tc activity leading to incorrect estimates of the percentage of the various impurities.

4.1.3 Comparison of the two methods

A comparison of the results of analysis of a number of ^{99m}Tc samples for radionuclidic impurities by the ionisation chamber and the gamma spectrometric methods is given in Table 4.

TABLE 4

COMPARISON OF RESULTS OF IMPURITY DETERMINATIONS FROM IONISATION CHAMBER AND GAMMA SPECTROMETRIC METHODS

Sample No.	Per cent ^{99}Mo		Per cent ^{132}I		Per cent ^{103}Ru	
	Ion Chamber	γ-Spectrometer	Ion Chamber	γ-Spectrometer	Ion Chamber	γ-Spectrometer
1	0.0030	0.0016	0.0070	0.0081	-	-
2	0.0027	0.0024	0.0032	0.0025	0.0003	0.0001
3	0.0028	0.0032	0.040	0.059	0.013	0.0040
4	0.0058	0.0019	0.0017	0.0019	0.0001	0.0001
5	0.0048	0.0050	0.074	0.096	-	-
6	0.0057	0.0077	0.0015	0.0013	-	-
7	0.17	0.14	0.0096	0.0085	0.025	0.0170
8	0.016	0.0098	0.0040	0.0040	0.0018	0.0013
9	0.023	0.021	0.0080	0.0092	0.0047	0.0037
10	0.16	0.12	0.027	0.038	0.042	0.0320
11	-	-	0.0010	0.0010	0.0003	0.0002
12	-	-	0.15	0.22	0.033	0.034
13	0.32	0.31	0.21	0.22	0.032	0.023
14	0.017	0.0094	0.0049	0.0026	0.0008	0.0002
15	-	-	0.0045	0.0039	0.0003	0.0020
16	-	-	0.0026	0.0018	-	-
17	0.067	0.061	0.015	0.021	0.010	0.009
18	0.031	0.037	0.033	0.043	0.0028	0.0043
19	-	-	0.035	0.043	0.0058	0.0009
20	0.069	0.086	0.078	0.068	0.0013	0.0013
21	0.035	0.031	0.0096	0.023	0.016	0.0140
22	0.050	0.049	0.0080	0.012	0.013	0.0130
23	0.14	0.14	0.0096	0.0092	-	-
24	0.054	0.037	0.0075	0.0070	0.0015	0.0002
25	0.12	0.095	0.089	0.096	0.016	0.008

The impurity levels of ^{131}I and ^{140}La were not determined by the ionisation chamber method. However, they were routinely determined by the gamma spectrometric method. Typically the results were $^{140}La < 0.0001$ per cent and $^{131}I < 0.0005$ per cent. The assumption made in the ionisation chamber method, that the samples

under analysis contained only ^{99m}Tc, ^{99}Mo, ^{132}I and ^{103}Ru, was essentially valid and introduced little error.

For ^{99}Mo, the linear correlation coefficient was found to be 0.98 and the least squares regression line could be expressed by

$$y = 1.05x + 3 \times 10^{-3} \text{ per cent}$$

where y = ion chamber result
x = γ-spectrometric result.

A Student 't' test to determine the significance of the calculated regression coefficients indicated that the value of 1.05 was not significantly different from unity. Hence it was assumed that a one to one correlation existed between the two methods. However, the value of the residual, 3×10^{-3} per cent, indicates that the correlation was valid only for impurity levels above 0.01 per cent.

For ^{132}I, the linear correlation coefficient was found to be 0.99 and the least squares regression line

$$y = 0.82x - 1 \times 10^{-3} \text{ per cent}$$

where y and x have the same meaning as before.

The test for significance showed that 0.82 was significantly different from 1.00. From this it appeared that the two methods were consistent but that the ion chamber result for ^{132}I tended to be lower by about 20 per cent. The value of the residual 1×10^{-3} per cent, indicated that the correlation of the values extended down to the 0.005 per cent impurity level.

The ionisation chamber method measured all long-lived fission products present as ^{103}Ru and it was envisaged that this assumption would be highlighted in the statistical analysis of the compared results. However the linear correlation coefficient was 0.96 and the least squares regression line could be expressed by

$$y = 1.16x + 1.1 \times 10^{-3} \text{ per cent}$$

where y and x had the same meaning as before.

The 't' test showed that there was no significant difference between the value of the calculated coefficient 1.16 and theoretical 1.00. The value of the residual, 1.1×10^{-3} per cent again showed that the correlation could be extended down to the 0.005 per cent impurity level.

Provided that the attenuation factors and the detection efficiencies for the various gamma rays of interest are accurately known, the gamma spectrometric method is a direct measurement of disintegration rates and may be considered almost as an absolute purity determination. It is estimated that the results obtained from it can be quoted with an accuracy of ± 20 per cent at the 90 per cent confidence level. However, since the method requires equipment which may not be readily available to the nuclear medicine department of a hospital it would almost certainly interest only generator producers.

The alternative ionisation chamber method is much simpler and requires equipment commonly found in the laboratories of all users of radionuclides. It depends on prior qualitative knowledge of the impurities present in the ^{99m}Tc since the timing of the individual measurements is influenced by the various half-lives. Other practical disadvantages are that the final result is not available for 7 days and that the measurement is subject to a higher error. It has been estimated that the error in a quoted result would be in the range ± 35 per cent to ± 60 per cent. These figures were obtained by combining the individual errors from the various measurements and they are inherently high because very small differences are involved in the calculation.

The capacity of the ionisation chamber method to resolve the components of complex radionuclide mixtures is limited. The gamma spectrometric method can be extended to include a wide range of γ-emitting radionuclides, the limiting factor being only the statistical significance of counts in any pre-selected peak.

Despite the many disadvantages of the ionisation chamber method, comparative statistical assessment of the results showed extremely good agreement for ^{99}Mo, ^{132}I and ^{103}Ru. However, the gamma spectrometric method is recommended because of its speed, range of application and sensitivity.

4.2 Chromatographic Separation of Radionuclide Impurities

The above measurements of radionuclidic purity were performed on aliquot samples of the total eluate from ^{99m}Tc generators. To examine whether some separation might occur between ^{99m}Tc and its major radiocontaminants during the elution process, the eluate from several generators was collected in 1 ml fractions. The radionuclidic purity of each fraction was examined to clarify the fine detail of the elution process. Because 25 samples needed to be measured at each elution, the ionisation chamber method was used so that all samples could be measured at approximately the same time. Generators of at least 500 mCi activity were used to improve accuracy. The results in Figure 4 show that ^{99}Mo, ^{103}Ru and ^{132}I were all eluted well before ^{99m}Tc. The most important consequences of this are that:

(i) If the first few ml of the elution process is used for analysis the result will not be representative.

(ii) Regardless of the levels of the radiocontaminants, these can be reduced with a small loss of ^{99m}Tc by discarding say the first 6 ml of the eluate.

This type of chromatographic separation was common to all generators examined and was repeated in the daily elutions of any one generator.

A large proportion of the ^{99}Mo and ^{103}Ru was associated with a breakthrough of finely divided alumina in the first few ml of eluate; these radiocontaminants were readily removed by filtration. However, the ^{132}I activity was not reduced by filtering and hence must have been in solution. The regular daily regeneration of the radiocontaminants obviously ruled out a simple "wash out" effect and even the passage of 1 litre of eluant through the generator did not prevent the radiocontaminants reappearing the next day in the first 6 ml of eluate.

It was concluded that the alumina breakthrough was caused by radiation damage to the large alumina particles of the absorbent bed, probably by the β-emission from ^{99}Mo. The effect was also observed after autoclaving when large quantities of finely divided alumina were produced as degradation products of the bed.

The regeneration of soluble ^{132}I in sequential elutions could be explained on the hypothesis that the generator contained a small amount of absorbed ^{132}Te which would yield its daughter product ^{132}I on treatment with saline.

Table 5 illustrates the typical regeneration of radionuclidic impurities in a sequence of daily elutions.

TABLE 5

TYPICAL REGENERATION OF IMPURITIES

Day	Sequential Eluant Volume (ml)	Per cent ^{99}Mo	Per cent ^{132}I	Per cent ^{103}Ru
1	* 6	7.68	0.94	0.43
	19	0.025	0.019	0.0012
Generator standing unused for 24 hours				
2	6	0.63	0.22	0.034
	19	0.0024	0.0025	0.00012

continued ...

TABLE 5 (continued)

Day	Sequential Eluant Volume (ml)	Per cent ^{99}Mo	Per cent ^{132}I	Per cent ^{103}Ru
Generator standing unused for 24 hours				
3	6 19	0.31 0.0024	0.22 0.0026	0.023 0.00015
Generator standing unused for 24 hours				
4	6 19	0.095 0.0019	0.096 0.0019	0.008 0.0001

* The combined effect of autoclaving and standing over the weekend

Table 6 shows the effect of passing the eluate through a 0.45 μm membrane filter.

TABLE 6

THE EFFECT OF A MEMBRANE FILTER

Sample unfiltered			Sample filtered		
^{99}Mo	^{132}I	^{103}Ru	^{99}Mo	^{132}I	^{103}Ru
0.081	0.005	0.010	0.001	0.005	0.0001

Thus radionuclidic impurities can be removed from the eluted ^{99m}Tc by discarding the first few ml of the eluate or by passing the total eluate through a 0.45 μm membrane filter.

4.3 Radiological Significance of Impurities

Wagner (1968) states that the use, on humans, of generator produced ^{99m}Tc is prohibited by the USAEC unless it can be shown that radionuclidic impurities are less than the following:

^{99}Mo	1 μCi/mCi	^{99m}Tc
^{103}Ru	0.1 μCi/mCi	^{99m}Tc
^{132}Te (^{132}I)	0.1 μCi/mCi	^{99m}Tc
^{131}I	0.1 μCi/mCi	^{99m}Tc

Even in terms of a direct comparison of impurity levels, the standard of the A.A.E.C. product is higher than that set by the USAEC. However, a more valid comparison is one based on the total radiological dose delivered. We have calculated whole body and specific organ doses for a radionuclide mixture equivalent to the USAEC maximum permitted concentrations and for a typical sample of A.A.E.C. generator produced ^{99m}Tc.

The doses were calculated by the method of Lovenger and Berman (1968) using the suggestions of Cloutier and Watson (1969) that for radionuclides uniformly distributed in the blood, the dose to any organ is due to the blood present in that organ at any given time, plus a contribution from other organs and the blood in the circulatory system.

Table 7 shows the calculated dose for the whole body, liver, spleen, lungs, kidneys and brain for an injection of each mixture. The USAEC purity requirements allow the radionuclidic impurities to contribute an additional 20 per cent to the incurred radiological dose. The impurity levels in the A.A.E.C. product add only a further 2 per cent to the radiological dose.

5. RADIOCHEMICAL PURITY

Three techniques were used to examine the radiochemical purity of eluted ^{99m}Tc solution:

(i) Ascending paper strip chromatography with 95 per cent methanol as the developing solvent.

(ii) Ascending cellulose thin layer chromatography with 95 per cent methanol as the developing solvent.

(iii) Paper strip electrophoresis using 0.001M sodium chloride as the electrolyte.

Special precautions were taken to minimise dissolved or adsorbed oxygen in the solvent systems and supporting materials and eluate samples were collected in a nitrogen atmosphere.

Active species on the supporting medium were located by cutting the paper strips or the thin layer sheets into 1 cm portions and then counting each portion in a scintillation counter set on the ^{99m}Tc peak.

Samples obtained by eluting the generator with saline, pH 5.5 and 9.5, isotonic sodium sulphate, pH 5.5 and 9.5 and 0.1N hydrochloric and sulphuric

TABLE 7

CALCULATED DOSE FOR AN INJECTION OF ^{99m}Tc SOLUTION

Radio-Nuclide	(RADS) Whole Body Dose		(RADS) Liver		(RADS) Spleen		(RADS) Lungs		(RADS) Kidneys		(RADS) Brain	
	USAEC mpc	A.A.E.C.	USAEC mpc	A.A.E.C.	USAEC mpc	A.A.E.C.	USAEC mpc	A.A.E.C.	USAEC mpc	A.A.E.C.	USAEC mpc	A.A.E.C.
^{99m}Tc	0.157	0.157	0.220	0.220	0.440	0.440	0.500	0.500	0.320	0.320	0.042	0.0420
^{99}Mo	0.014	0.002	0.026	0.004	0.086	0.010	0.052	0.006	0.040	0.005	0.002	0.0002
^{131}I	0.003	Neg.*	0.005	Neg.	0.013	Neg.	0.009	Neg.	0.006	Neg.	0.001	Neg.
^{132}I	0.0001	Neg.	0.0002	Neg.	0.0006	Neg.	0.0004	Neg.	0.0004	Neg.	0.0006	Neg.
^{140}La	-	Neg.	-	Neg.	-	Neg.	-	Neg.	-	Neg.	-	Neg.
^{103}Ru	0.010	0.00015	0.017	0.0002	0.035	0.0006	0.024	0.0004	0.020	0.0003	0.006	0.0001
Total Dose (RADS)	0.184	0.159	0.268	0.224	0.575	0.457	0.581	0.506	0.386	0.325	0.052	0.0423
Total Dose from non ^{99m}Tc Components	0.027	0.002	0.048	0.004	0.135	0.010	0.085	0.006	0.066	0.005	0.010	0.0003

USAEC mpc 10 mCi ^{99m}Tc 10 μCi ^{99}Mo
1 μCi ^{103}Ru 1 μCi ^{132}I
1 μCi ^{131}I

A.A.E.C. 10 mCi ^{99m}Tc 1.4 μCi ^{99}Mo
0.015 μCi ^{103}Ru 0.07 μCi ^{132}I
0.003 μCi ^{131}I 0.01 μCi ^{140}La

* Negligible - less than 0.0001 RADS

acid, pH 1.0, were compared against a pertechnetate standard produced from sublimed Tc_2O_7. Sodium sulphate was used as an alternative to saline to determine the effect of chloride ions on the radiochemical form of ^{99m}Tc.

With the exception of the 0.1N HCl and 0.1N H_2SO_4 eluates, each sample showed a narrow well defined peak, corresponding to the pertechnetate species, containing more than 98 per cent of the activity. For the strongly acid eluates the pertechnetate peak was also evident but it was accompanied by a long tail and a minor peak at the origin. When these samples were adjusted to pH 5.5 with sodium hydroxide, aluminium hydroxide was precipitated. Radiochemical analysis of the neutral supernate showed only the simple pertechnetate chromatographic pattern.

Since this effect was noticed in both the chloride and sulphate eluates and since it was unaffected by the presence of added oxidising agents it was deduced that the atypical chromatograms for the acid eluates were caused by sparingly soluble or colloidal alumino-technetium compounds/complexes.

Anders (1960) has reported that concentrated hydrochloric acid will reduce Tc(VII) to Tc(IV) although the reaction is slow and proceeds through several intermediate oxidation states. However, in our analyses there were no significant indications of a difference in technetium species for the 0.1N HCl and 0.1N H_2SO_4 eluates.

Finally there was no indication that the special precautions taken in the preparation of the materials of analysis or the method of collecting the eluate under nitrogen, were necessary for satisfactory radiochemical analysis.

6. CHEMICAL PURITY

The principal undesirable chemical contaminant in eluted ^{99m}Tc solutions is aluminium. As described earlier a breakthrough of insoluble aluminium (hydrated oxide) is responsible for much of the radionuclidic impurity present in the solution; it occurs in the first few ml eluted and can be conveniently separated either by discarding the early eluate volumes or by passing the eluate through a membrane filter.

There is also a small soluble aluminium component which has recently been cited as the cause of difficulties experienced in the preparation of certain ^{99m}Tc-labelled compounds. For example Weinstein and Smoak (1970) have reported that soluble aluminium will cause agglutination of red blood cells if it occurs in the ^{99m}Tc-labelling solution in concentrations as low as 5 µg per ml. The USAEC has specified, presumably on the basis of aluminium toxicity, that soluble aluminium should not exceed 50 µg per mCi ^{99m}Tc. Hence if the eluate from a generator is arbitrarily assumed to have a

radioactive concentration of 10 mCi ^{99m}Tc per ml, the USAEC specification would permit the soluble aluminium content to approach 500 µg per ml, that is, 100 times the level known to cause erythrocyte agglutination in vitro.

Because of the apparent discrepancy between the 'legal' and the practical requirements it was decided to study the various factors that might affect aluminium contamination.

The filtered eluates from a series of generators were examined for aluminium content; the results were assessed to determine the influences of the activity of the generator, the age of the generator and its history of previous use.

Soluble aluminium was determined colorimetrically by the method of Pakalns (1965), using the dye Chrome Azurol S and the results are shown in Tables 8 and 9. The random distribution of the results in Table 8 suggests that aluminium contamination is not dependent on generator activity. However a general reduction in aluminium levels was evident in successive elutions (Table 9). To determine whether this phenomenon was time or volume related a fresh generator was eluted with 175 ml saline with samples being taken for analysis after every 25 ml. The results for these samples are shown in Table 10.

TABLE 8

THE SOLUBLE ALUMINIUM CONTENT OF ELUATES OBTAINED ON THE FIRST DAY OF GENERATOR USE

Activity of Generator (mCi ^{99}Mo)	Al^{3+} Concentration* (µg/ml)
252	36
236	36
1,650	84
2,250	19
3,500	8
857	75
133	21
543	22
30	41
28	32
68	92

* Eluant volume was 25 ml saline

TABLE 9

THE SOLUBLE ALUMINIUM CONTENT OF SEQUENTIAL ELUTIONS

Sample	Day	Al^{3+} Concentration* (µg/ml)
1	Monday	36
	Tuesday	10
	Wednesday	6
	Thursday	< 5
	Friday	< 5
2	Monday	75
	Tuesday	20
	Wednesday	9
	Thursday	< 5
	Friday	< 5

* Eluant volume was 25 ml saline

TABLE 10

THE EFFECT OF ELUANT VOLUME ON SOLUBLE ALUMINIUM CONCENTRATION

Day	Eluant Volume (ml saline)	Al^{3+} Concentration (µg/ml)
1	25	83
2	25	30
	25	13
	25	8
	25	< 5
	25	< 5
3	25	< 5

Again, a gradual reduction in soluble aluminium content was observed with increasing eluant volumes and after 100 ml had passed through the generator the level had dropped to less than 5 µg per ml. Allowing the generator to stand for a further 24 hours before eluting again did not give rise to a

significant increase in soluble aluminium content. Hence there is a difference between the mechanisms of formation of soluble and insoluble aluminium contamination. As mentioned earlier, there is a daily regeneration of insoluble aluminium which we presume to be caused by radiation damage to the generator bed. It appears that soluble aluminium is produced by the initial passage of the strongly acid ^{99}Mo loading solution through the aluminium oxide bed. The aluminium ions formed at this time are subsequently washed out in a quasi-exponential pattern, with the concentration in the eluate being reduced by half for every 20 ml of eluant.

7. BIOLOGICAL PURITY

The main criteria of biological purity of solutions to be administered parenterally are sterility and freedom from pyrogens; these requirements are equally applicable to sodium pertechnetate solutions eluted from ^{99m}Tc generators although the mode of preparation is, in a pharmaceutical sense, unique.

In a discussion of quality control of radiopharmaceuticals, Charlton (1966) stated that one difficulty of generator systems is that final control is not in the hands of the manufacturer but of the user, whose resources are often more limited. It remains however the responsibility of the manufacturer to design generator systems that can be kept sterile and pyrogen free with wide margins of safety without the need of elaborate handling procedures.

The production of technetium generators at the A.A.E.C. was described in Section 2. Stringent quality control procedures are applied to maintain biological purity in both materials and equipment. Empty generator vials are cleaned in pyrogen free water and then heated in dry air at 160°C for 1 hour. The chromatographic grade alumina is digested for several hours in 1M nitric acid and just before insertion into the generator bottles it is autoclaved at 132°C for 6 minutes. The alumina is quickly transferred into the generator bottles and washed with a sterile pyrogen free solution of 1M nitric acid to remove any fines. The assembly is then capped and sealed at both ends of the bottle.

For the last step in the preparation of the ^{99}Mo stock solution, pyrogen free water is used to dilute the nitric acid to 1 molar concentration. The generator is loaded via a 23 gauge hypodermic needle in the top rubber stopper. The effluent passes out via a second needle at the base. The generator is finally flushed through with 250 ml of sterile, pyrogen free and isotonic solution of sodium nitrate and then the needles are removed.

The generator is sterilised by autoclaving at 121°C for 33 minutes, the efficacy of the autoclaving process being monitored by a parallel non-radioactive

'generator' into which has been inserted a spore strip of B. stearothermophilus. After the autoclaving process the spore strip is removed aseptically from the dummy generator and transferred to a bottle containing dextrose - tryptone broth in which it is incubated at 55°C for 96 hours. Satisfactory sterilisation is indicated only by the complete absence of bacterial growth.

Sterility was confirmed by incubation in a thioglycollate medium at 37°C for 14 days. No aerobic or anaerobic bacterial growth was observed for the ^{99}Mo loading solution or the ^{99m}Tc solutions from autoclaved and non-autoclaved generators.

The chemical processes and production techniques adopted give a pyrogen free eluate. This may be due to the use of alumina as the absorbent bed, since filtration through an alumina bed is an effective method of removing pyrogens.

8. CONCLUSION

We have defined the various parameters governing performance and quality control and described the methods used in the assessment of the A.A.E.C. fission based ^{99m}Tc generator.

The mechanism relating milking efficiency to eluant pH is not well understood. There is a clear indication that autoclaved generators are less efficient than the non-autoclaved variety.

The major impurities in the eluate are ^{99}Mo, ^{132}I and ^{103}Ru, and these can be removed, or reduced to insignificant levels by discarding early eluate volumes. By modifying the processing of the ^{99}Mo loading solution the last traces of $^{132}Te/^{132}I$ can be removed.

Two methods (ionisation chamber and gamma spectrometry) of determining radionuclidic contamination are suited to the measurement of the critical levels of contamination. Gamma spectrometry has also been successfully applied to very pure ^{99m}Tc solutions.

A radiological assessment of the significance of the radionuclidic impurities in eluted ^{99m}Tc solutions shows that very little additional dose would be delivered by the extraneous fission products.

Under the usual conditions of elution, ^{99m}Tc is almost exclusively in the pertechnetate form. The chemical species observed in solutions obtained from acid elutions show slight differences but these are not due to the presence of lower valency states; rather the results obtained indicate the presence of modifying alumino-complexes.

A chemical purity examination which concentrated on the measurement of aluminium content clearly showed the need for thorough pre-washing of the generator before use.

The results of sterility and pyrogen testing prove that the generator design and the method of producing and loading the ^{99}Mo solution yield a biologically pure product. Provided that bacterial contamination is excluded by proper handling techniques there would appear to be no real justification for terminal autoclaving.

In summary the limitations on the medical use of the fission based ^{99m}Tc generator, as produced by the A.A.E.C. are very slight indeed. The fears expressed elsewhere of gross fission product contamination have no foundation in respect of A.A.E.C. generators. Hence the advantages of the small bed generator containing carrier free ^{99}Mo can be fully realised in almost complete safety.

9. ACKNOWLEDGEMENTS

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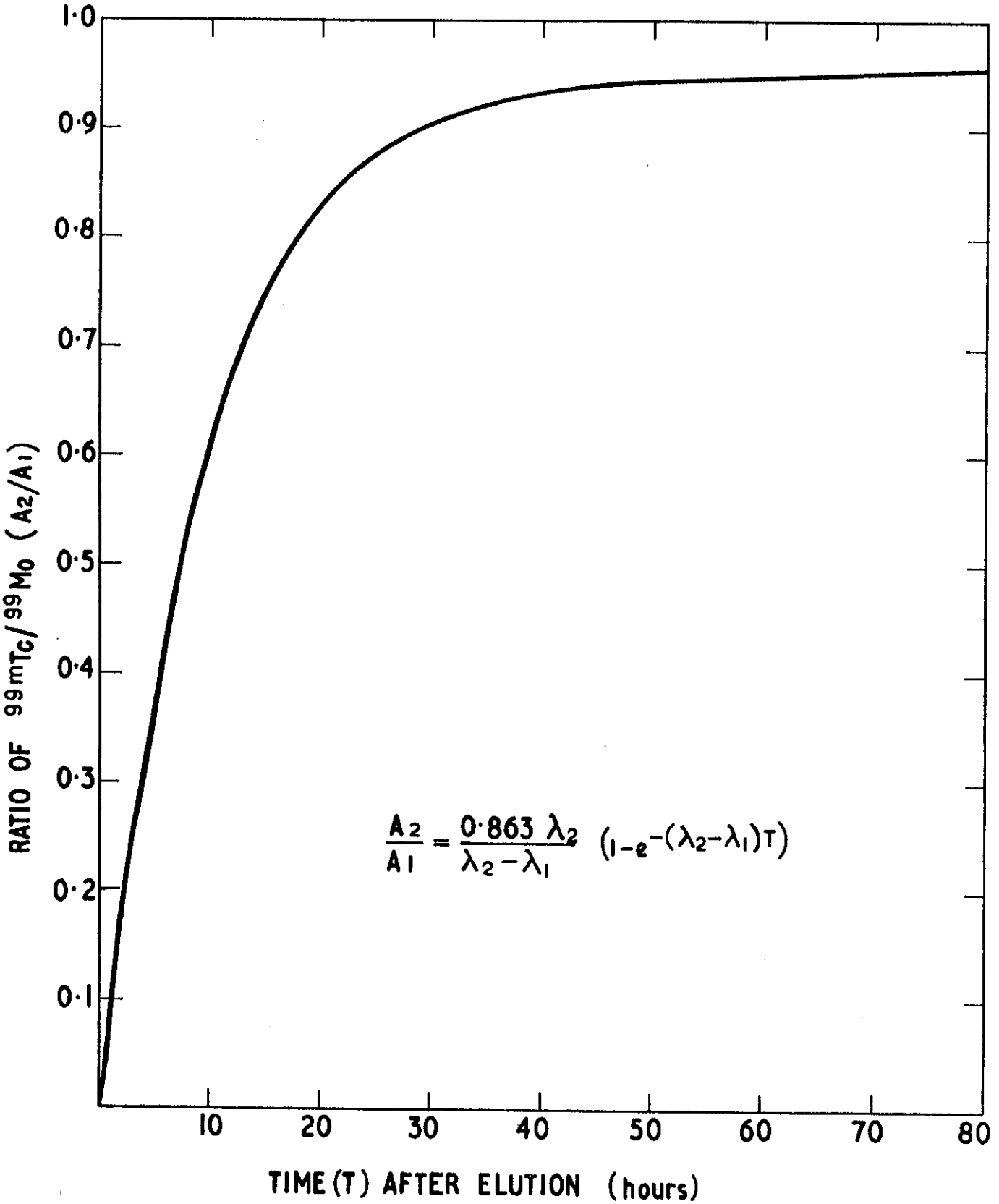

FIGURE 1. TIME DEPENDENCE OF THE $^{99m}Tc/^{99}Mo$ RATIO

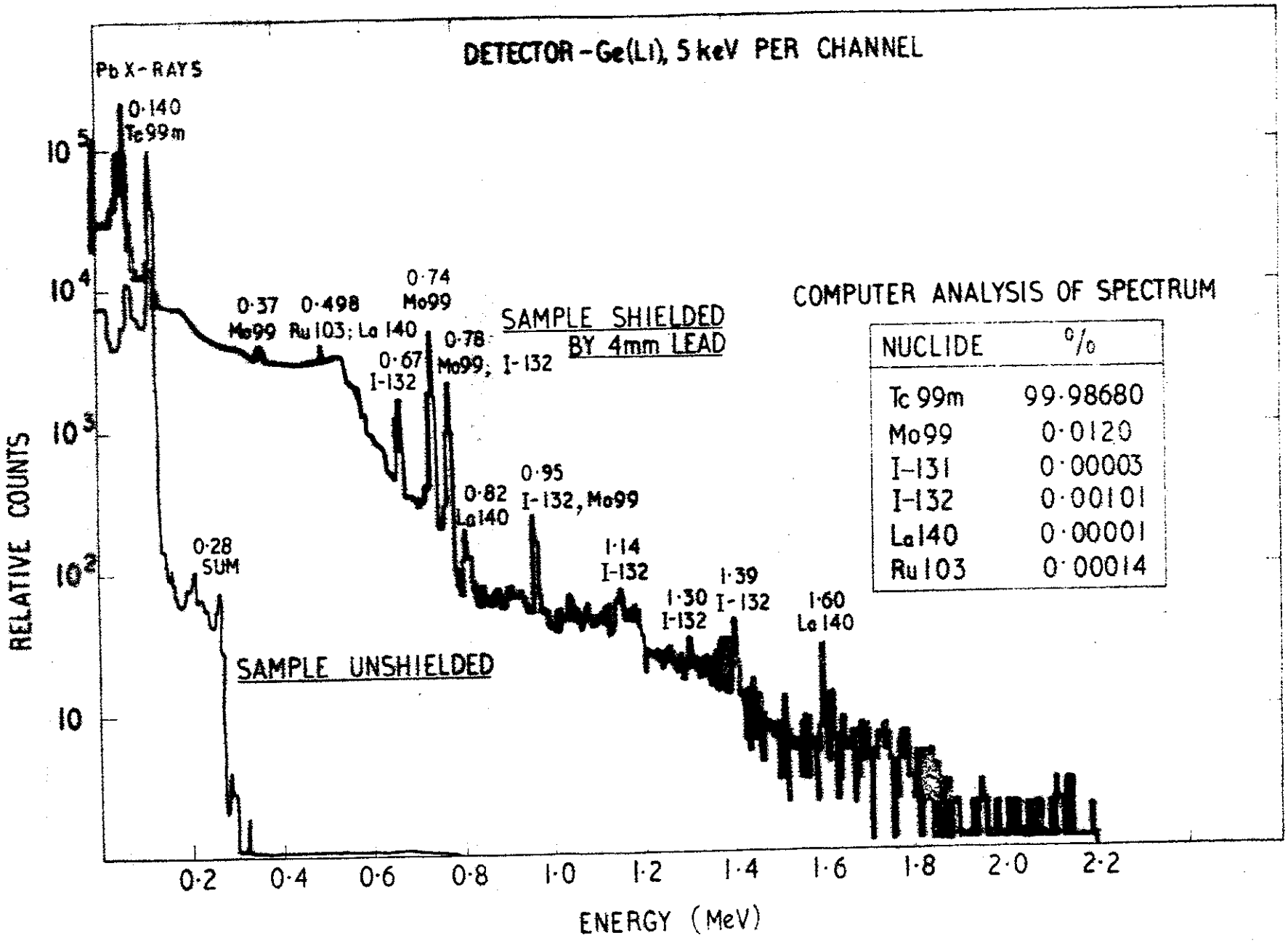

FIGURE 2. SAMPLE SPECTRAL RESPONSE (Ge (Li) DETECTOR)

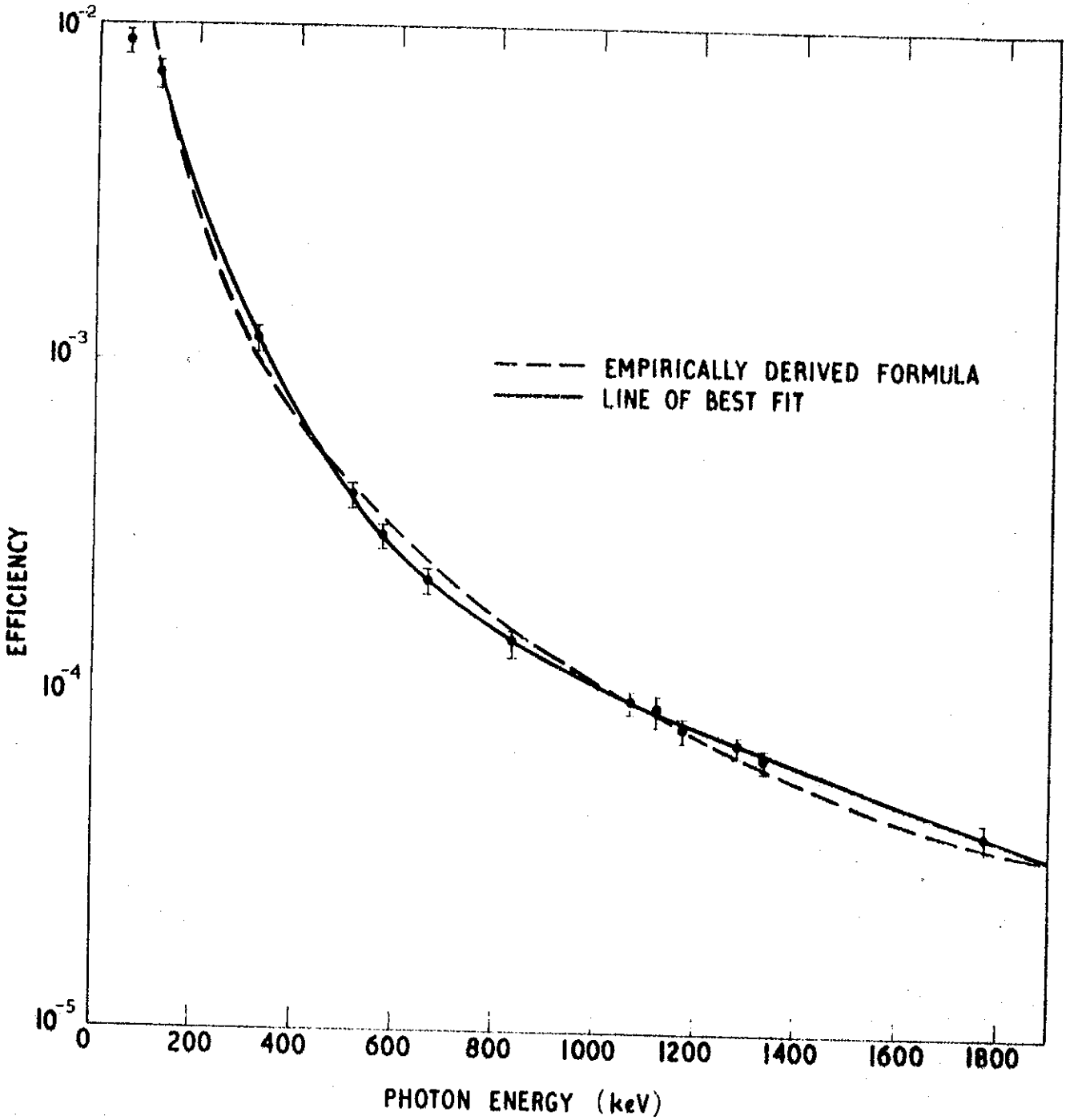

FIGURE 3. Ge (Li) DETECTOR EFFICIENCY AS A FUNCTION OF PHOTON ENERGY

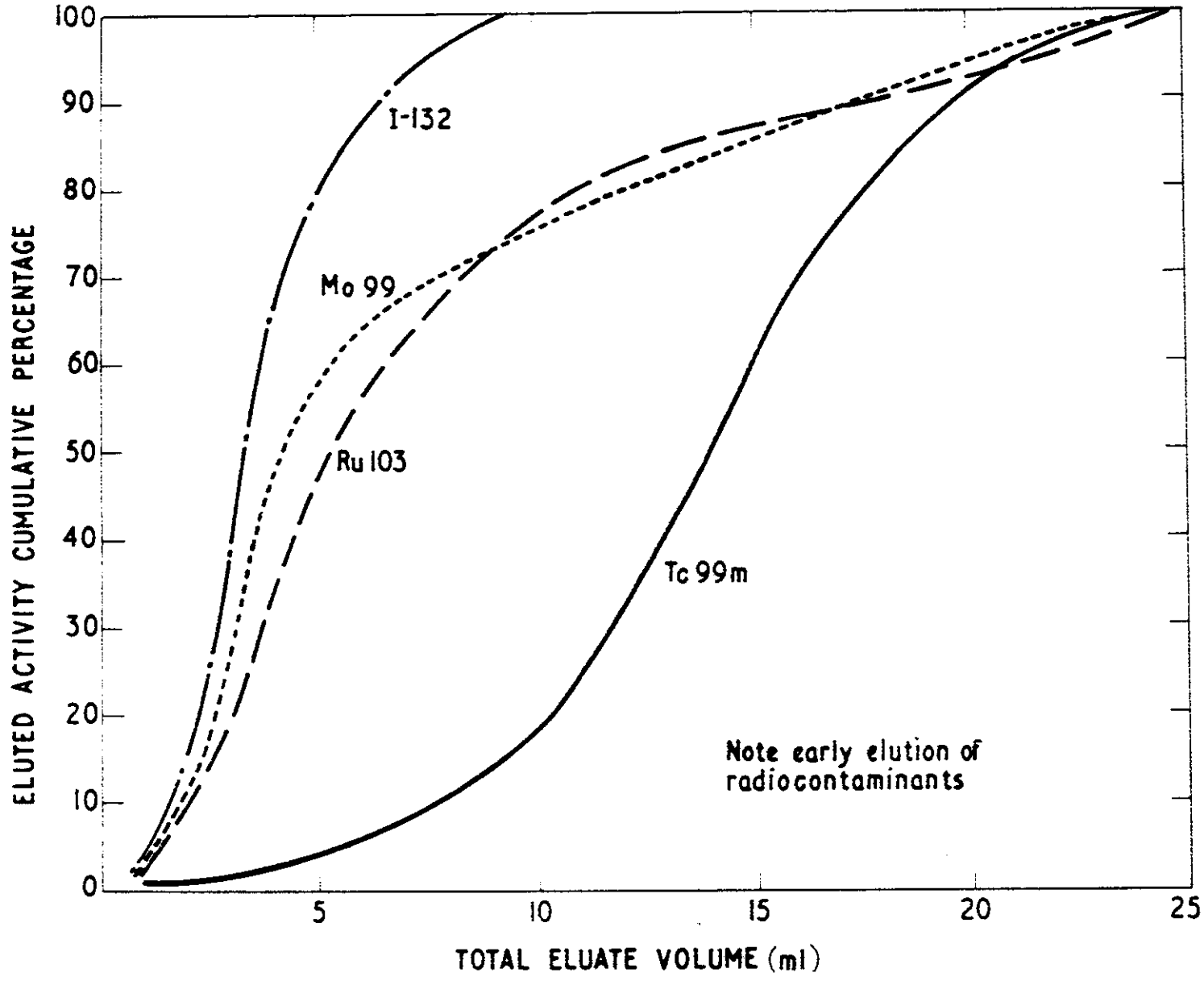

FIGURE 4. ELUTION CHARACTERISTICS OF A GENERATOR