The use of ^{99m}Tc as a tracer in the determination of ^{99}Tc by ICP-mass spectrometry

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Full Paper

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The aim of this paper is to carry out a deep study on the possibilities of using ^{99m}Tc from ^{99}Mo–^{99m}Tc clinical isotope generators to trace the radiochemical separations for ^{99}Tc measurements by ICP-MS. By appropriately defining a minimum detectable mass concentration (MDMC) for the mass spectrometer it is possible to conclude that such use is acceptable for a wide range of activities of the tracer. The MDMC increases from 0.41 to 0.51 ppt when the amount of ^{99m}Tc added to the samples ranges from 0 to 2 MBq. The purification of the final sample from Ru must be the main objective of the ^{99}Tc measurement method, since its presence noticeably enhances the ^{99}Tc MDMC.

1 Introduction

^{99}Tc is a pure beta-emitter, $E_{max} = 294$ keV, with a long half-life of 2.11×10^5 y. It can be considered as an extinct radionuclide although there is some experimental documentation on its natural production during the spontaneous fission of ^{238}U in uranium ores.[1]

Nevertheless, ^{99}Tc has been reintroduced into nature during the nuclear era, since it is also produced during the fission of ^{235}U and ^{239}Pu at a rate of an average of 6%, very similar to that of ^{137}Cs. It is estimated that some 15 PBq have been produced throughout the nuclear fuel cycle.[2] About 10% has been released into the environment which masks any ^{99}Tc trace of natural origin. Nuclear military tests have released an additional quantity of 140 TBq mainly into the atmosphere.

The environmental relevance of ^{99}Tc is well recognised, as its long half-life assures its presence in nature for a long time. This fact makes ^{99}Tc a significant radionuclide for future nuclear waste management, as well as an important contributor to the committed dose of radiation to the population. In addition, ^{99}Tc is considered a good potential tracer of some environmental processes such as marine water movements.

Despite this fact, there is no ample Tc environmental data archive. This lack of documentation is not surprising considering the difficulty in determining its environmental concentrations. Sub-ppt ^{99}Tc levels in non-perturbed sites pose serious limitations on the use of traditional radiometric methods for its determination (1 mBq g^{-1} ^{99}Tc = 1.6 pg g^{-1}). It is true, however, that some of these methods, developed during the early eighties, were able to produce a relevant ^{99}Tc data file.[2–4] Nevertheless, some environmental issues still remain unexplored for ^{99}Tc and only the recent use of mass spectrometry has enabled the scientific community to meet the experimental challenge of ^{99}Tc determination at very low levels.

ICP-MS,[5] RIMS[6] and even accelerator mass spectrometry (AMS)[7] have been used to determine ^{99}Tc in a variety of environmental samples. Comparisons between radiometric and non-radiometric methods have also been carried out.[8] In all cases, source preparation requires more or less intensive radiochemistry to avoid isobaric interferences, or to condition the sample in the ion source. Consequently, it is necessary to use a tracer to calculate the yield obtained after sample preparation.

^{95m}Tc, ^{97m}Tc or even ^{99m}Tc are good candidates as tracers in Tc chemical extractions and, in fact, all of them have already been used in connection with radiometric methods. ^{99m}Tc could be a good option as it is very easy to obtain. However, it does not seem the best choice when using ICP-MS, at least from a formal point of view, because ^{99}Tc is its daughter product. In principle, this could lead to interferences in the sample measurements. ^{95m}Tc ($T_{1/2} = 61$ days) is the most suitable radiochemical tracer for mass spectrometric measurements, due to its convenient long half-life and the absence of possible mass interferences. Nevertheless, some authors claim that commercially available solutions of ^{95m}Tc contain considerable amounts of ^{99}Tc.[9] The same scientists propose the production of laboratory-made solutions of this radionuclide using the reaction ^{95}Nb(α,2n)^{95m}Tc. However not all the laboratories have access to such facilities and easier alternatives such as that of ^{99m}Tc should be explored.

In this paper, we will study in depth the advantages and disadvantages of using ^{99m}Tc as a tracer for sample preparation in ICP-MS. Several ^{99m}Tc solutions obtained from isotope generators in general use in nuclear medicine are studied by using ICP-MS. The objective is to determine to what extent it is possible to use ^{99m}Tc as a tracer for sample preparation, and what kind of limitations are introduced on the sensitivity of the method.

2 The spectrometer

The ICP-MS system used is a Hewlett-Packard 4500 (Yokogawa Analytical Systems, Tokyo, Japan). Tuning of the system is accomplished by minimising the so called instrumental limit of detection (LOD) defined as:

$$\text{LOD} = \frac{3\sigma_B}{S - B}c \qquad (1)$$

where σ_B is the standard deviation of the counts obtained in the blank during a given integration time, 10 s in our case, c is the mass concentration of the standard used for tuning, S is the

number of counts under the mass peak of interest and B the background counts of the process obtained during blank measurement runs.

Our system can perform an automatic tuning for the complete mass range (7–254 u). Using the optimum set of operational parameters, the LOD for ^{99}Tc reaches a value of 46 ppt. A complete account of the tuning process for ^{99}Tc can be found in the thesis of J. L. Mas.[10] The following is a short description.

A complete series of optimisation experiments with a solution of ^{99}Tc containing 65.4 ± 1.1 ppm diluted in deionized water (DAMRI, Gif-sur-Yvette Cedex, France) to obtain 13.1 ± 0.3 ppb were carried out. The first stage of the experiments consisted of the application of the variable control method to check the dependence of the S/B on several operational parameters: rf power, carrier gas flow, sampling depth and ion lens voltages. By maximising the S/B a set of operational parameters was found which gave an instrumental LOD of 0.2 ppt for ^{99}Tc.

To check the suitability of the achieved working conditions, a direct search method was used to optimise the S/B by applying Spendley's Simplex[11] to five lenses of the ion optics system: the extraction lens 1, the Einzel plate 2, the bias omega lens, the omega minus lens and the quadrupole focus lens. During that optimisation run, the set of operational parameters and mechanical variables previously found, were kept constant.

The Simplex was carried out by adapting the algorithm from the Numerical Recipes in Pascal to our working conditions. As can be seen in Fig. 1, there is a fast convergence towards a S/B peak. With the obtained conditions an operational LOD of 0.8 ppt was found. It is clearly lower than that found by automatic tuning and is equivalent to the value obtained during the tuning of the mechanical variables. The final set of parameters is listed in Table 1. The LOD is an operational limit of detection which serves to optimise the system for ^{99}Tc counting, in our case. A more realistic and fundamental approach to the problem of detection limits and minimum detectable concentrations is given in Section 5.

3 Samples: preparation and measurement

^{99m}Tc samples were obtained from a ^{99}Mo–^{99m}Tc clinical isotope generator, Amertec (Amersham, Buckinghamshire, UK). As usual ^{99m}Tc was eluted from an alumina chromatographic column into a physiological serum solution in 0.9% NaCl.

Consecutive elutions were carried out after each 20–24 h from the same isotope generator. Typically, the eluate volume was 5 ml, with the exception of one sample in which the volume was 12 ml (see next Section).

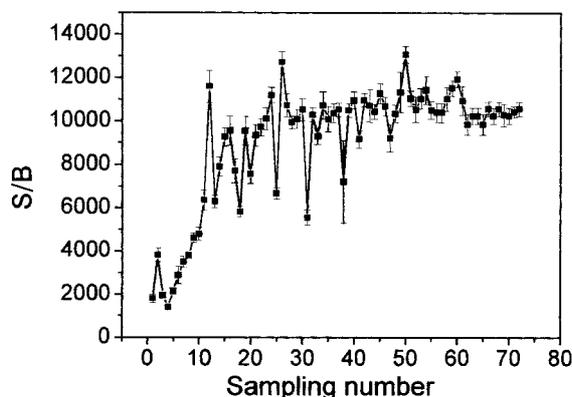In Fig. 2 the theoretically expected time evolution of the

Fig. 1 S/B evolution with the 5-D Spenley's Simplex to tune the ion optics.

Table 1 Operating conditions for ICP-MS

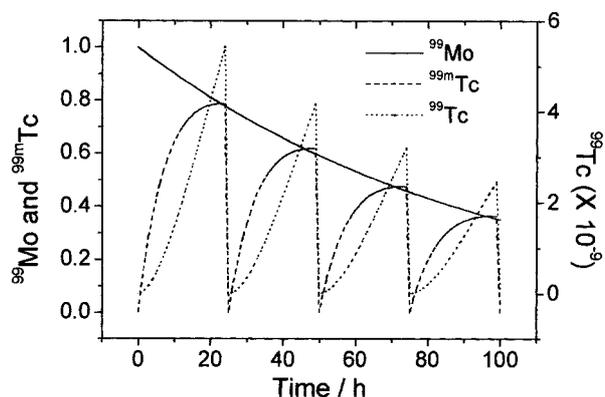| Rf power | 1240 W |
Coolant gas flow	$15 \, l \, min^{-1}$
Carrier	$1.17 \, l \, min^{-1}$
Nebulizer	Babington type
Sampling depth	6 mm
Extraction lens 1	-150 V
Einzel 2 lens	5.5 V
Bias omega lens	-51 V
Omega minus lens	-3 V
Quadrupole focus	6 V

Fig. 2 Theoretical predictions of normalized (to ^{99}Mo) activities on the column. The continuous line represents the ^{99}Mo activity time evolution. Dotted lines give the ^{99m}Tc and ^{99}Tc activities time evolution.

^{99}Mo activity contained in the isotope generator is plotted. The predicted behaviour of the ^{99m}Tc activity present in the generator is given, which includes the periodic cut-offs produced in the growth of the activity due to the elutions. All the results were obtained by applying the well known Bateman equations:

$$a_1 = a_{1,0} e^{-\lambda_1 t} \tag{2}$$

$$a_2 = \frac{\lambda_2 a_{1,0}}{\lambda_2 - \lambda_1}(e^{-\lambda_1 t} - e^{-\lambda_{12} t}) \tag{3}$$

$$a_3 = \lambda_2 \lambda_3 a_{1,0}$$
$$\times \left[\frac{e^{-\lambda_1 t}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{e^{-\lambda_2 t}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{e^{-\lambda_3 t}}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} \right] \tag{4}$$

a_1 and $a_{1,0}$ being the specific activities at time t and $t = 0$ for the ith radionuclide, λi (h^{-1}) its decay constant and t the time. The subindices 1, 2, 3 correspond to ^{99}Mo, ^{99m}Tc and ^{99}Tc, respectively. ^{99m}Tc in the eluate was left to decay for at least two weeks. In this way the health risks associated with the handling of such high activity samples were avoided. The ^{99m}Tc activity was previously measured by NaI(Tl) γ-spectrometry (EG&G ORTEC, Nuclear Ibérica S.A., Madrid, Spain) and the eluate activity concentration at the time of elution was determined.

Once the ^{99m}Tc had totally decayed, the ^{99}Tc mass and activity concentrations were determined using our ICP-MS system with optimum counting conditions. The solutions were diluted nine-fold in 5% HNO_3 before measurement by ICP-MS in order to avoid matrix effects from the massive presence of NaCl in the eluate, which could block the extraction cones. Deionized water ($>18 \, M\Omega \, cm$) and supra-pure grade HNO_3 (Merck, Darmstadt, Germany) were used for the dilution.

Table 2 ^{99}Tc and ^{99m}Tc activity concentrations in the eluates obtained at different elution times from the first elution. Relative uncertainties of ^{99m}Tc activity concentrations range from 1–3%

Time/hours	^{99}Tc activity concentration/Bq g^{-1}	^{99m}Tc activity concentration/MBq g^{-1}
0	9.2 ± 0.3	1422.6
21.0	7.3 ± 0.3	596.4
46.5	14.4 ± 0.2	977.5
69.0	9.7 ± 0.2	781.2
141.0	19.5 ± 0.6	394.9
167.2	4.87 ± 0.11	285.6
190.2	3.1 ± 0.1	214.6
213.9	2.4 ± 0.1	168.7
237.7	2.0 ± 0.1	128.1
309.9	3.96 ± 0.14	65.8
331.4	0.75 ± 0.02	45.8
357.7	0.68 ± 0.04	35.4
380.9	0.49 ± 0.02	27.5

4 Results

In Table 2 the ^{99m}Tc and ^{99}Tc activity concentrations in the different eluates are presented. Time origin was taken at the first elution instant. Thus, the meaning of time in Table 2 is "time elapsed from the first elution". The results are plotted in Fig. 3. ^{99m}Tc activity follows an exponential decay law with the half-life of ^{99}Mo, as is expected. With the exception of the two first points, the rest perfectly fit to an exponential decay law ($r^2 = 0.9996$), with $a_0 = (1.58 \pm 0.02) \times 10^9$ Bq g^{-1} and $T_{1/2} = 67.4 \pm 1.4$ h. Sample 2 does not follow general behaviour, because the elution volume was 12 ml (see previous Section) instead of 5 ml, the physiological serum volume used for the rest of samples. The consequence was a higher dilution factor for the obtained activity and, therefore, a smaller activity concentration than expected. It is evident that a simple volume normalisation would permit the inclusion of such data into the general exponential curve.

After the first elution, the correlation among the ^{99m}Tc and ^{99}Tc activity concentrations in the eluate is very clear, with the exceptions of samples 5 and 10. It can be seen in Table 2 that, in both cases, the time elapsed from the previous elution was larger than normal. In fact they were collected after a week-end waiting time period. The consequence is an increase of the ^{99}Tc activity in the generator which is recovered in the following elution. This can be predicted by the Bateman equations, as seen in Fig. 4, where we depict the experimental time evolution of the ^{99}Tc activity concentration together with the predictions of eqn. 3. To carry out the calculations, the ^{99}Mo initial activity was assumed to be that of ^{99m}Tc in the first eluate, instead of the ^{99}Mo activity which appears in the isotope generator description. This last activity is normally given with a very high
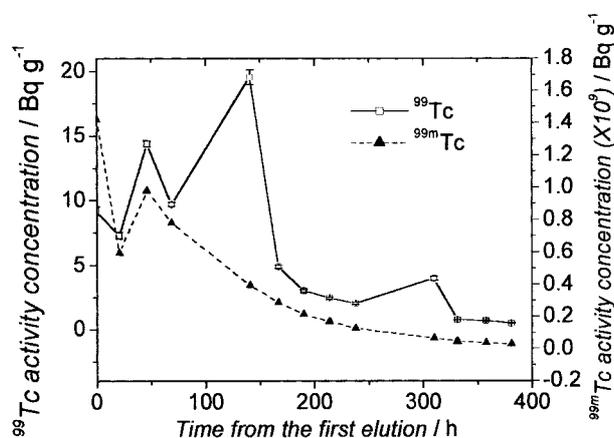

Fig. 3 Time evolution of activities on the chromatographic column. Lines are depicted to guide the eye.
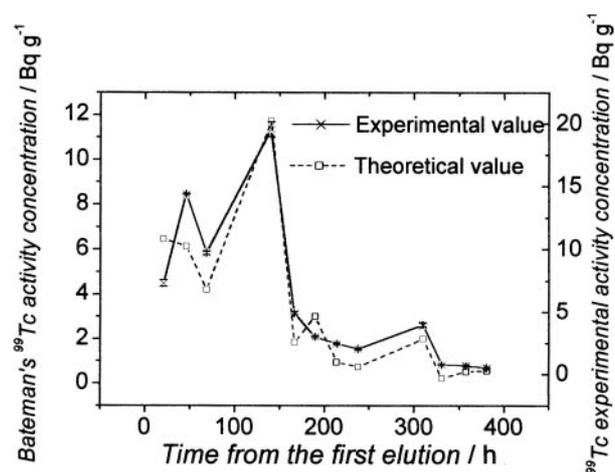

Fig. 4 Theoretical and experimental values of ^{99}Tc specific activity.

uncertainty. The assumption is perfectly reasonable since both ^{99}Mo and ^{99m}Tc are in secular equilibrium before the first elution.

The time used in eqns. 2–4 is the time elapsed between elutions. For every calculation, $a_{1,0}$ is supposed to be that of ^{99}Mo activity in the previous elution. In addition $a_{2,0}$ and $a_{3,0}$ are 0. The agreement between the experimental values and the theoretical predictions is clear although the experimental values systematically exceed the theoretical ones. That excess can be explained on the basis of the elution recovery yield for ^{99}Tc. Theoretically it is supposed that 100% of the ^{99}Tc present in the column is recovered, whereas it is more realistic to suppose that some ^{99}Tc remains in the column after each elution. The amount recovered in the following elution is contributing to an increase in the ^{99}Tc activity concentration.

The ^{99}Tc accumulation effect is perfectly coherent with the predictions of eqn. 4. It is observed that the maximum ^{99m}Tc activity in the column is obtained at $t = 23.5$ h. After such a time the negative term in eqn. 4 dominates and the activity of the daughter product, ^{99}Tc, increases. This can also be seen when studying the time evolution of the ^{99}Tc/^{99m}Tc activity ratio in the eluates (plotted in Fig 5, together with the experimental data).

All these results are very relevant if ^{99m}Tc from clinical isotope generators is going to be used for tracing radiochemical extractions for ICP-MS measurements. It is clear that previous to the elution of ^{99m}Tc which will be taken for tracing, the accumulated ^{99}Tc has to be removed from the generator. Therefore, a prior elution step is compulsory.

A given amount of ^{99}Tc is added to the sample during the spiking process; theoretically some 5 pg of ^{99}Tc is added to the sample per MBq of ^{99m}Tc. Or in real terms, according to our experimental results, some 10 pg of ^{99}Tc per MBq of ^{99m}Tc are added to trace the separation, i.e., twice the theoretical expected result.

This has to be taken into account in the calculation of the ^{99}Tc concentration in the real sample, and, of course, it affects the LOD of the procedure as can be seen in the following Section.

5 Limits of detection

It is apparent that the LOD is sample-dependent and has to be reformulated. According to Currie[12] the detection limit, LOD, can be written as follows:

$$\text{LOD} = 2.54(1 + \sqrt{1 + 2.48\sigma_0^2}) \qquad (5)$$

at a confidence level of 0.05 for the I- and II-species errors with σ_0 being the standard deviation of a null response.
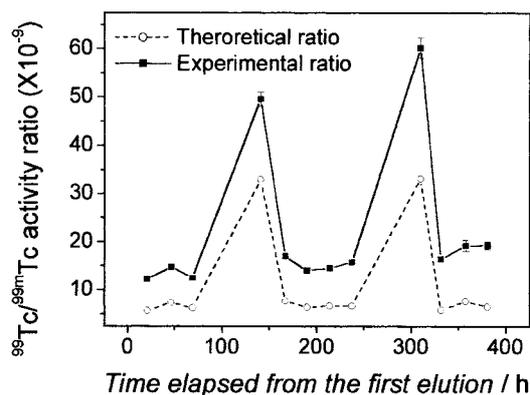
Fig. 5 Time evolution of the activity ratios.

Fig. 6 MDMC and backgound increment dependence on tracer activity added.

Fig. 7 ^{99m}Tc MDMC and equivalent Ru concentration dependence on the standard deviation at $m/z = 102$.

Several contributions have to be taken into account in order to evaluate σ_0; firstly, the background B due to aleatory counts, photons, overlaps from ^{100}Mo on mass 99 (due to abundance sensitivity), ^{98}MoH generation, electric noise, *etc.*, obtained in a blank procedure sample in the absence, of course, of the tracer. In our working conditions the net counting due to abundance sensitivity could be 1–2 orders of magnitude higher than the contribution from hydride generation.[10] On the other hand, the isotopic abundance of ^{98}Mo is more than twice that of ^{100}Mo natural abundance. Thus, special care must be taken to purify the sample from Mo.[8]

A second contribution comes from the ^{99}Ru present in the sample, the reagents or internal standard, which cannot be totally removed with the chemical procedure. This contribution is sample-dependent and can be estimated by checking the presence of other Ru isotopes, *i.e.*, ^{101}Ru or ^{102}Ru, in the mass spectrum. The most traditional choice is ^{101}Ru, as we used in this work, although ^{102}Ru could be alternatively used provided there is no Pd in the final sample. The well known atomic abundance ratio between ^{99}Ru and ^{101}Ru allows its estimation from the counts obtained in the ^{101}Ru mass region, S_{Ru-101}. Finally, the ^{99}Tc added to the sample as a consequence of the use of ^{99m}Tc as tracer, S_{Tc-99m}, is sample-dependent and will also vary according to the chemical recovery of the separation procedure, R_Q.

Therefore, the gross background response B_t at a given integration time becomes:

$$B_t = B + \alpha S_{Ru-101} + S_{Tc-99m} = B + \frac{12.6}{17.8} S_{Ru-101}$$
$$+ \frac{R_Q T_{1/2}^{99m} a_t m_t M}{N_A m_s \ln 2} b \qquad (6)$$

where $T_{1/2}^{99m}$ is the half-life of ^{99m}Tc, a_t its specific activity added to the sample to measure R_Q, M its molar weight (99 grams), N_A the Avogadro's number, m_t the mass of the tracer added to the sample, m_s the sample mass, and b the slope of the calibration curve of the ICP-MS system.

Consequently, the net response in an experimental measurement would be:

$$S = S_g - B - 0.708 \, S_{Ru-101} - \frac{R_Q T_{1/2}^{99m} a_t m_t M}{N_A m_s \ln 2} b \qquad (7)$$

where S_g is the total number of counts under the ^{99}Tc mass peak. For a null response the value of σ_0 can be calculated by applying the error propagation formula:

$$\sigma_0 = \sqrt{ \sigma_B^2 + (0.708 \, \sigma_{Ru-101})^2 + \left(\frac{T_{1/2}^{99m} M a_t m_t b R_Q}{N_A m_s \ln 2} \right)^2 \times \left[\left(\frac{\sigma_{RQ}}{R_Q}\right)^2 + \left(\frac{\sigma_{at}}{a_t}\right)^2 + \left(\frac{\sigma_{mt}}{m_t}\right)^2 + \left(\frac{\sigma_b}{b}\right)^2 + \left(\frac{\sigma_{ms}}{m_s}\right)^2 \right] } \qquad (8)$$
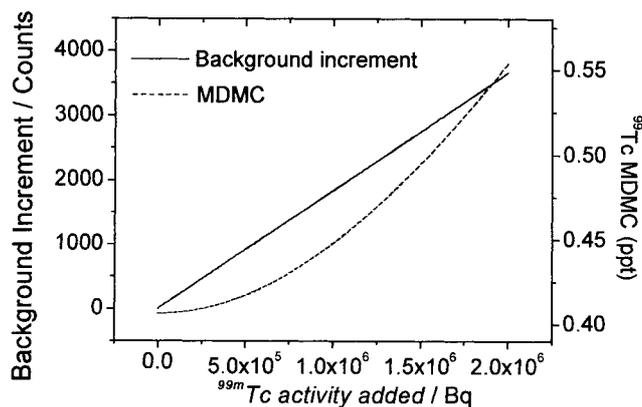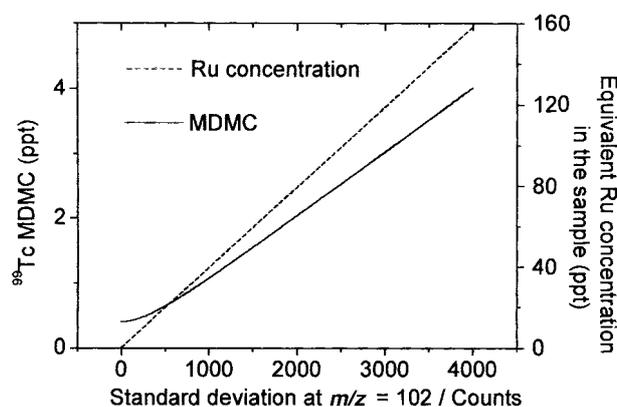
The full mathematical expresion for the LOD can be easily written from the above equation. To quantify the capabilities of the method we define a minimum detectable mass concentration, MDMC, as

$$\text{MDMC} = \frac{\text{LOD}}{b} \qquad (9)$$

where $b = 1600$ counts ppt^{-1} and is the slope of the calibration curve of our system for the typical working conditions.

The influence of the MDMC of the ^{99m}Tc activity, in Bq (added to trace the sample) is depicted in Fig. 6. An integration time of 10 s was taken, which supposes that $\sigma_B = 160$ counts. On the other hand, a value of $\sigma_{Ru-101} = 45$ counts, a normal value, was fixed for the calculations. Finally R_Q was assumed to be 100%, the worst case, although, unfortunately, from another point of view, the less frequent case. With these values a MDMC of 0.41 ppt in the absence of tracer can be calculated. Within a range of 0 to 2 MBq, the MDMC changes from 0.41 to 0.55 ppt, *i.e.*, a 34% relative variation. It seems clear that the modification of the MDMC is not very important and, within a reasonable range of tracer activity from 0 to 100 kBq, the variation is irrelevant. This means that, under our experimental conditions, the influence of the tracer is almost negligible, at least in the presence of the assumed Ru contamination.

The influence of σ_{Ru-101}, as seen in Fig. 7, is more important. The calculations have been performed for a constant tracer activity of 50 kBq, and the above mentioned values for the rest of variables. The plot shows that the need for refining the radiochemical methodology to purify the sample from Ru is a key point with regard to the sensitivity of the method. It is even more important than the influence of the amount of ^{99m}Tc added to the sample, provided the guidelines given in the

previous section on the use of the generators are followed. Indeed a change in σ_{Ru-101} from 0 to 1000 counts, which is equivalent to a range of Ru contamination from 0 to 70 ppt, produces a relative variation in the MDMC of some 455%, which could be significant in many applications.

6 Conclusions

Measurements of the concentration of ^{99}Tc in eluates from ^{99}Mo–^{99m}Tc clinical isotope generators have been carried out. Results have been compared to the predictions from Batemann equations. An algorithm has been developed for the calculation of detection limits in the determination of ^{99}Tc by ICP-MS. The algorithm can be easily extended to other problems in which the presence of interferences could affect the determination of the nuclide of interest.

It can be concluded that, under well defined working conditions, the use of ^{99m}Tc from clinical isotope generators to trace the radiochemical separation for the measurement of ^{99}Tc by ICP-MS is acceptable. Within a wide range of ^{99m}Tc activities, the added tracer does not appreciably change the minimum detectable ^{99}Tc concentration of the method. It is more important, however, to decontaminate the sample from Ru carefully, because its presence noticeably enhances the minimum determination level.

Acknowledgements

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