Primary standardization and half-life determination of ^{225}Ac at NRC

Galea, R.; Moore, K.

Publisher's version / Version de l'éditeur:
https://doi.org/10.1016/j.apradiso.2023.111105
Applied Radiation and Isotopes, 203, C, pp. 1-6, 2023-11-08

Primary standardization and half-life determination of ^{225}Ac at NRC

R.Galea[1,], K.Moore[1]

[a]*National Research Council of Canada, 1200 Montreal Road, Ottawa, K1A0R6, ON, Canada*

Abstract

A solution of ^{225}Ac was standardized by NRC using the triple-to-double coincidence ratio (TDCR) method. The counting efficiencies were calculated assuming a counting efficiency of 100% for alpha decays and those calculated using the MICELLE2 Monte Carlo code for beta decays and was approximately 500% for the NRC TDCR system. The relative uncertainty for the activity concentration was determined to be 0.25%. This agreed with measurements performed using gamma spectroscopy and a predicted calibration factor for the Vinten 671 ionization chamber as calculated using an EGSnrc model, implementing radioactive decay. Finally, the half-life of ^{225}Ac was determined from long-term measurements using ionization chambers and liquid scintillation counting. The NRC measured half-life for ^{225}Ac was found to be 9.914(4) days and is consistent within an expanded uncertainty coverage of k=2 with the most recent (**?** **?**]) measurements of this decay parameter.

Keywords: ^{225}Ac, targeted alpha therapy, half-life

1. Introduction

Targeted alpha therapy (TAT) is an increasingly important treatment method in nuclear medicine (**?**]). Due to their high linear-energy transfer, alphas deliver their therapeutic power within a very short distance which causes maximal damage to targeted cells while minimizing effects on healthy tissues. In addition, a wide range of radioligands are becoming available that specifically target over-expressed receptors in tumor cells. One such important TAT isotope is Actinium-225 (^{225}Ac). ^{225}Ac, in radioactive equilibrium with its progeny, can deliver multiple alphas to targeted cancer cells. This isotope can be produced via multiple methods, all of which will need calibration to evaluate delivery doses for clinical trials or to evaluate production modes.

*Corresponding author

The National Research Council of Canada (NRC) performed a standardization of ^{225}Ac, from a source provided by Canadian Nuclear Laboratories (CNL), which uses a more traditional ^{229}Th generator approach to the production of ^{225}Ac (**?**]). The activity concentration of this source (^{225}Ac in radioactive equilibrium and in liquid form) was standardized at NRC by means of the Triple-to-Double Coincidence Ratio (TDCR) method. The total efficiency of ^{225}Ac in equilibrium with its progeny was calculated using the MICELLE2 code (**?**]).

The current half-life cited in the Decay Data Evaluation Project (DDEP) for ^{225}Ac is 10.0(1) d (**?**]). However, more recent and more precise measurements have been published by **?**] and **?**]. Hence, this work also determined the half-life of ^{225}Ac, which agrees well with the more recent measurements of this important nuclear decay parameter.

2. ^{225}Ac standardization

2.1. Sample preparation

A single sample was provided for this work from CNL, and arrived in the form of Actinium Nitrate ($^{225}Ac(NO_3)_3$) in 0.1 M nitric acid. From this parent material, traceable serum vials were produced by gravimetric means for measurement in the NRC Secondary Standard Ionizing Radiation Chamber System (**?**]) (SSIRCS), which is comprised of mutliple ionization chambers (ICs), some of which were used in long-term half-life measurements for ^{225}Ac and described below.

Dilutions of the parent material were made and used in the production of two sets of six quenched liquid scintillation counting (LSC) vials. The LSC samples consisted of 20 mL borosilicate glass vials filled with 15 mL of liquid scintillator cocktail Ultima Gold AB. Two additional unquenched samples were prepared using Ultima Gold and no additional water was added. Finally, a matching blank sample was made using 0.1 M nitric acid. The gravimetric measurements used approximately 20 mg of solution in each sample vial and this was determined by NRC traceable measurements on a Mettler XP26 microbalance. Nitromethane was added to these samples to act as a chemical quench and to provide a variation in the counting efficiency. These samples were counted in a Hidex 300SL-METRO counter for 600 s each with 10 repetitions. The chemical quench did not induce a large variation in the TDCR parameter, (from 0.9803-0.9924) as one would expect given that large number of αs. A lineage diagram summarizing the sample preparation for this measurement campaign is shown in Fig. **??**.

Thin film mylar sources were also produced to check for radioactive impurities and measured using a high purity germanium detector (Mirion GX8020). The spectra were analyzed

over the measurement campaign and no gamma emitting impurities beyond the expected progeny of the ^{225}Ac were detected.

2.2. Efficiency calculation

^{225}Ac decays through a cascade of six shorter-lived radioactive progeny isotopes to ^{209}Bi (Fig. **??**), whose half-lfe is $(1.9(2) \times 10^{19}$ a) (**?**]) and is considered stable in the context of this analysis. The counting efficiencies of the alpha decays were assumed to be unity ($\epsilon_\alpha = 1$) and the beta decay counting efficiencies coming from ^{213}Bi, ^{209}Tl and ^{209}Pb were calculated using the MICELLE2 code (**?**]) which implements a free parameter model (**?**]). The counting efficiencies for the individual nuclide α/β transitions was calculated as follows:

$$\epsilon_{nucl}(\lambda) = P_{\alpha/\beta} \cdot k \cdot \epsilon_{\alpha/\beta}(\lambda), \tag{1}$$

where $P_{\alpha/\beta}$ is the probability of an α/β decay per parent ^{225}Ac decay, k denotes the equilibrium factor with respect to the parent ^{225}Ac, $\epsilon_{\alpha/\beta}$ is the counting efficiency (which is calculated for logical sum of double coincidences (doubles) and triple coincidences (triples) in the TDCR detector) and λ is the free parameter.

The equilibrium factors were calculated by several methods, using the Bateman equations (**?**]), recursively as in **?**], but also using an open source python package (**?**]) called radioactivedecay. The difference between the calculations was not significant. The open source python package contained decay data that was not consistent with the DDEP (**?**]). Nevertheless, the result was consistent with a variation of the nuclear decay data due to their respective uncertainties when solving the Bateman equations.

A correction for the short-lived progeny of ^{217}At and ^{213}Po, with half-lives of 32.3(4) ms and 3.70(5) μs respectively, was adopted from **?**]. The efficiency of detection for the short-lived ^{217}At and ^{213}Po require a correction as some decays of this isotope can take place during the counter dead time, t_{dead}. The correction is approximated as :

$$k_{\mathrm{At/Po},survival} = exp\left(-ln(2)\frac{t_{dead}}{\tau_{1/2}(^{217}\mathrm{At}/^{213}\mathrm{Po})}\right), \tag{2}$$

where At/Po and $\tau_{1/2}(^{217}\mathrm{At}/^{213}\mathrm{Po})$ correspond to the calculation of the survival factor and half-life value for ^{217}At or ^{213}Po respectively. For a fixed dead time of 30 μs, the survival factor for ^{217}At and ^{213}Po are 0.999356 and 0.003624 respectively.

Given the extremely short half-life of ^{213}Po, the decays of ^{213}Bi and ^{213}Po can be considered jointly as in **?**], which derives the combined double and triple counting efficiency as

$$
\begin{aligned}
\epsilon_{D/T,^{213}\mathrm{(Bi+Po)}} =& \epsilon_{D/T,^{213}\mathrm{Bi}} \cdot k_{\mathrm{Po},survival} \cdot (1+\epsilon_\alpha) \\
&+ \epsilon_{D/T,^{213}\mathrm{Bi}} \cdot (1-k_{\mathrm{Po},survival}) \\
&+ (\epsilon_{S,^{213}\mathrm{Bi}} - \epsilon_{D,^{213}\mathrm{Bi}}) \cdot k_{\mathrm{Po},survival} \cdot \epsilon_\alpha \\
&+ (1-\epsilon_{S,^{213}\mathrm{Bi}}) \cdot \epsilon_\alpha,
\end{aligned} \tag{3}
$$

where the subscripts S,D,T correspond to singles, logical sum of doubles and triples respectively, $(\epsilon_{S,^{213}\mathrm{Bi}} - \epsilon_{D,^{213}\mathrm{Bi}})$ is the probability that a ^{213}Bi decay is counted only in a single PMT, and $(1-\epsilon_{S,^{213}\mathrm{Bi}})$ is the probability that a ^{213}Bi decay is not registered in any PMTs. Therefore the total efficiency for doubles and triples is given by equation **??**.

$$
\begin{aligned}
\epsilon_{D/T,total} =& \epsilon_\alpha \cdot (P_{\alpha,^{225}\mathrm{Ac}} \cdot k_0 + P_{\alpha,^{221}\mathrm{Fr}} \cdot k_1 + P_{\alpha,^{217}\mathrm{At}} \cdot k_2 \cdot k_{\mathrm{At},survival} + P_{\alpha,^{213}\mathrm{Bi}} \cdot k_3) \\
&+ P_{\beta,^{213}\mathrm{Bi}} \cdot k_3 \cdot \epsilon_{D/T,^{213}\mathrm{(Bi+Po)}} \\
&+ P_{\beta,^{209}\mathrm{Tl}} \cdot k_4 \cdot \epsilon_{D/T,^{209}\mathrm{Tl}} \\
&+ (P_{\beta,^{209}\mathrm{Tl}} \cdot k_5 + P_{\beta,^{213}\mathrm{Bi}} \cdot k_6) \cdot \epsilon_{D/T,^{209}\mathrm{Pb}}.
\end{aligned} \tag{4}
$$

Table **??** summarizes the coefficients used in equation **??**. For a TDCR value of 0.9886 the total doubles efficiency was calculated to be 4.9899 roughly translating to 500% efficiency as expected given the five αs and their progeny in the decay scheme of ^{225}Ac.

2.3. Activity concentration

Thin film point sources were made and measured in a calibrated high purity germanium detector. No γ-emitting impurities were detected from these measurements. Various samples were counted in the SSIRCS for 15-30 days and no indication of in-growth of ^{225}Ac was detected. This means that the ^{225}Ac was in secular equilibrium with its progeny at the time of measurement and that no significant Thorium-229 (^{229}Th) or Radium-225 (^{225}Ra), due to imperfect chemical separation of the parent ^{229}Th, was present in the samples.

Two liquid scintillation counting data sets were independently analyzed and agreed very well lending confidence to the primary activity concentration value determined to be 42.4(1) kBq/g (k=1). In addition, the γ spectra acquired during the impurity investigation permitted a quantification of the ^{225}Ac present in the sample and hence provided another comparison value. The 440.44(1) keV γ from Bismuth-213 and 218.12(2) keV (**?**]) γ from Francium-221 were used to recover the activity concentration, which was found to be 43.4(1.3) kBq/g (k=1). All of these results agreed within their respective expanded uncertainties at k=2 and their agreement is illustrated in Figure **??**. An EGSnrc (**?** **?**])

model was used to predict the calibration factor for a Vinten 671 IC, which is one of the SSIRCS ICs. This model prediction permitted a comparison value to be determined. While this model only agreed with the experimental determinations at the level of k=3, this was deemed sufficient for the purposes of comparison as the experimental values would be used to determine a calibration factor for this IC. However, further studies were performed that suggested a greater uncertainty due to the glass thickness of the vial in the model compared to reality but this has not been sufficiently benchmarked to be presented in this paper.

The uncertainties associated with the standardization process are summarized in the Table **??**. No radioactive impurities, other than those coming from the expected progeny, were detected in the γ-spectroscopy measurements performed throughout the measurement campaign. The efficiencies, calculated with the MICELLE2 code varied the value of the Birks parameter, kB, with insignificant effect and a value of kB=0.0075 cm·MeV^{-1} was adopted. Finally, the dead time of the Hidex 300SL-METRO counter was fixed at 30 μs and could not be varied. **?**] showed the effect of this experimental parameter on the analysis, mainly due to the loss of events coming from the decay of the very short lived ^{213}Po, but stability could be achieved with a dead time of at least 30 μs with an uncertainty of 0.1%.

The uncertainty assigned to a given measurement is the quadratic sum of all contributing statistical and systematic uncertainties.

3. ^{225}Ac half-life

The half-life of ^{225}Ac was determined at NRC using a serum vial[1] measured in an IC of the SSIRCS and also using the double and triple count rates of the unquenched LSC vials produced for the standardization. The summary of the results and the uncertainties associated with those measurements is given in Table **??**. The final half-life determined by NRC is compared with recent determinations of this parameter and is shown in Figure **??**. The ^{225}Ac half-life was determined by taking a weighted average of all three measurements summarized in Table **??** and resulted in a value of 9.914(4) d (k=1).

The TPA (**?**]) IC was used for the half-life measurement in which a serum vial was measured multiple times a day periodically, for a total time of 90 days (see Figure **??**). The data was fit over the entire 90 day dataset and multiple sub-ranges. The fit was performed as a linear fit model or an exponential decay model with or without a term for the background

[1]The serum vial used was a glass vial with a volume of 5 mL and was sealed with a rubber septum and crimped aluminum cap.

to determine the result. When correcting for the background, the background variation from quality control measurements made consistently on this IC was used along with the stability determined through long-term measurements of standards for this IC.

The unquenched LSC vials were also counted, initially for 10 days, and recounted a month later for 30 days in a Hidex 300SL-METRO. The samples were counted for 600 s and corrected for the background, which was counted at the same time as the ^{225}Ac LSC samples. The counting rate triples and doubles were fit as a function of the time since the first measurements. Both the doubles and triples were consistent with each other when extracting the half-life. The TDCR parameter was stable up to 60 days after the initial measurements at the level of 0.04%, calculated from the standard deviation of the TDCR parameter, as seen in the plot of the doubles residuals in Figure **??**. As in the case of the IC measurements, the fit ranges were varied and fit models were varied to study the robustness of the fit and the results are tabulated in Table **??**.

The final half-life determination used the full 90 day dataset from the IC measurements and the 30-60 day measurements of the LSC data.

4. Conclusions

^{225}Ac, in equilibrium with its progeny, was standardized at NRC using the primary TDCR method and found to be supported by an EGSnrc model of IC measurements and a secondary method of activity determination based on γ-spectroscopy. Its activity concentration was determined to be 42.4(1) kBq/g (k=1). Further comparison of the standardization of ^{225}Ac is important and hence so is participation in an international comparison of this isotope and/or submission of an ampoule to the SIR International Reference System. To date only two laboratories have submitted an ampoule of ^{225}Ac to the SIR (**?**]) and more are needed to strengthen the Key Comparison Reference Value for ^{225}Ac, a very important TAT radioisotope. Measurements of the half-life of ^{225}Ac were also performed, through measurements in an IC and a liquid scintillation counter. The NRC determined half-life for ^{225}Ac was 9.914(4) d (k=1) and was consistent with more recent measurements of this parameter in the literature. All recent measurements of the ^{225}Ac half-life indicate a smaller and more precise value than that currently recommended in the DDEP (**?**]).

5. Acknowledgements

The authors would like to thank CNL for providing the material for this important analysis and the authors of **?**] from which our analysis was influenced.

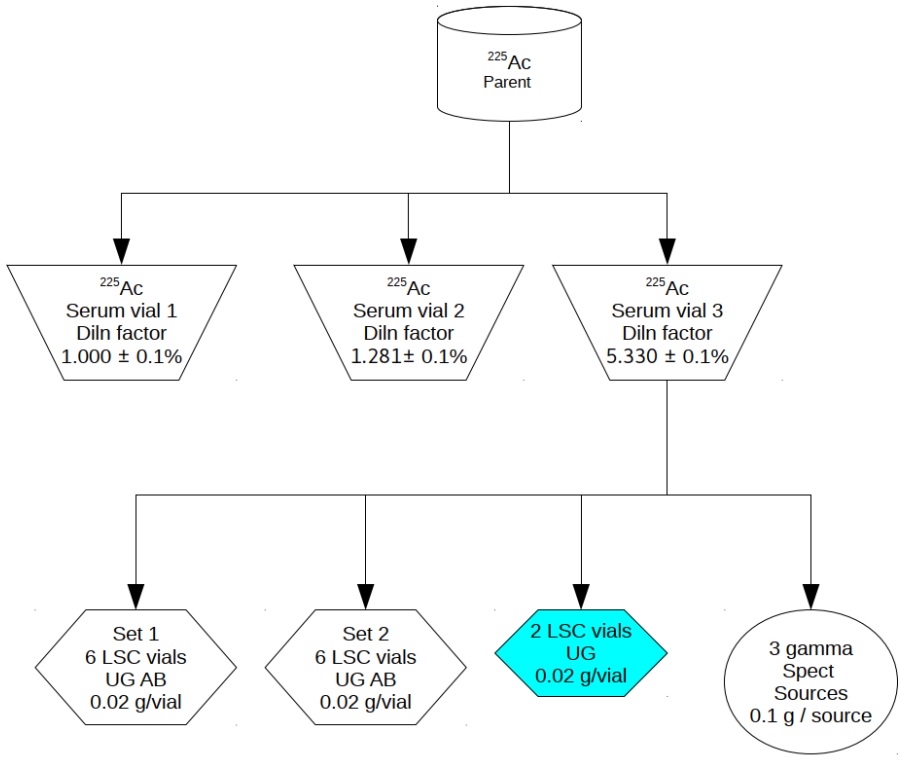

Figure 1: The sample preparation plan for the ^{225}Ac standardization campaign described in this paper. A series of three serum vials were initially prepared. Two of which were used for measurements in ICs and the third for the preparation of LSC counting samples and fixed point sources for γ-spectroscopy.

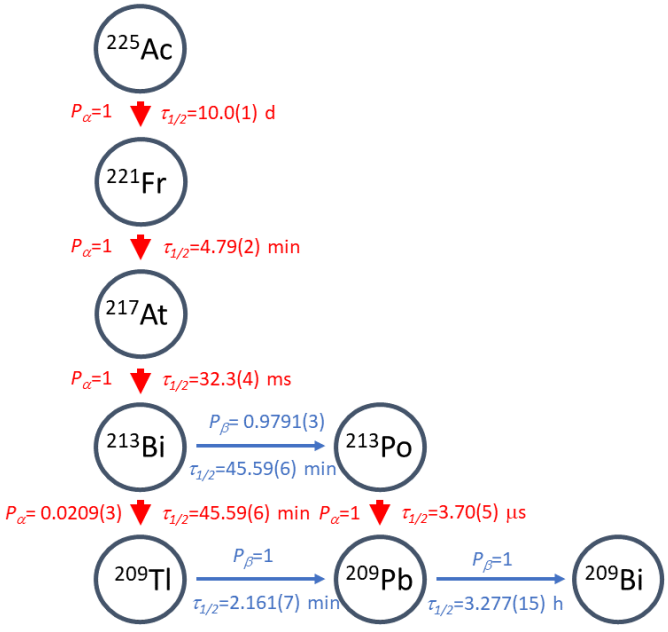

Figure 2: The decay chain of ^{225}Ac. γ emissions are not indicated in the figure.

Decay$_x$	Coefficient	$P_{\alpha/\beta}$	Equilibrium factor	ϵ_D	ϵ_x
$^{225}\mathrm{Ac} \xrightarrow{\alpha} {}^{221}\mathrm{Fr}$	$P_{\alpha,^{225}\mathrm{Ac}} \cdot k_0$=1.0000	$P_{\alpha,^{225}\mathrm{Ac}}$=1.0000	k_0=1.0000	1.0000	1.0000
$^{221}\mathrm{Fr} \xrightarrow{\alpha} {}^{217}\mathrm{At}$	$P_{\alpha,^{221}\mathrm{Fr}} \cdot k_1$=1.0003	$P_{\alpha,^{221}\mathrm{Fr}}$=1.0000	k_1=1.0003	1.0000	1.0003
$^{217}\mathrm{At} \xrightarrow{\alpha} {}^{213}\mathrm{Bi}$	$P_{\alpha,^{217}\mathrm{At}} \cdot k_2 \cdot k_{\mathrm{At},survival}$=0.9997	$P_{\alpha,^{217}\mathrm{At}}$=1.0000	$k_2 \cdot k_{\mathrm{At},survival}$=0.9997	1.0000	0.9997
$^{213}\mathrm{Bi} \xrightarrow{\alpha} {}^{209}\mathrm{Tl}$	$P_{\alpha,^{213}\mathrm{Bi}} \cdot k_3$=0.0210	$P_{\alpha,^{213}\mathrm{Bi}}$=0.0209(3)	k_3=1.0035	1.0000	0.0210
$^{213}\mathrm{Bi} \xrightarrow{\beta} {}^{213}\mathrm{Po}$	$P_{\beta,^{213}\mathrm{Bi}} \cdot k_3$=0.9825	$P_{\beta,^{213}\mathrm{Bi}}$=0.9791(3)	k_3=1.0035	1.0007**	0.9832
$^{209}\mathrm{Tl} \xrightarrow{\beta} {}^{209}\mathrm{Pb}$	$P_{\beta,^{209}\mathrm{Tl}} \cdot k_4$=0.0210	$P_{\beta,^{209}\mathrm{Tl}}$=0.0209(3)*	k_4=1.0037	0.9460	0.0198
$^{209}\mathrm{Pb} \xrightarrow{\beta} {}^{209}\mathrm{Bi}$	$P_{\beta,^{209}\mathrm{Tl}} \cdot k_5 + P_{\beta,^{213}\mathrm{Bi}} \cdot k_6$=1.0174	$P_{\beta,^{209}\mathrm{Tl}}$=0.0209(3)*	k_5=1.0176	0.9556	0.0203
		$P_{\beta,^{213}\mathrm{Bi}}$=0.9791(3)	k_6=1.0174	0.9556	0.9519
				$\epsilon_{D,Total}$	4.9963

Table 1: Constant coefficients in equation **??** for the calculation of the total efficiency. * ^{209}Tl decays via β emission 100% of the time but is expressed here as the probability of a ^{209}Tl β decay per decay of ^{225}Ac. This could alternatively be calculated into the equilibrium factors using the Bateman equation and then apply the $P_{\beta,^{209}\mathrm{Tl}}$=1.0000 but the result of the coefficient is equivalent. ** is calculated using equation **??**.

Uncertainty Component	Type	Relative Standard Uncertainty (%)
counting statistics	A	0.2
background	A	0.001
weighing	B	0.03
dead time	B	0.1
model & decay data	B	0.08
decay correction	B	0.1
impurities		none detected
Total:		**0.25%**

Table 2: Uncertainty budget for the primary activity measurements of the liquid sample.

Uncertainty Component	IC (%)	LSC(Doubles) (%)	LSC(Triples) (%)
Background	0.01	0.01	0.01
Fit range	0.02	0.02	0.04
Fit model	0.02	0.02	0.04
Linearity	0.06	0.01	0.01
Stability	0.05	0.04	0.04
Total: (k=1)	0.08	0.06	0.07
Total: (k=2)	0.16	0.12	0.14
$\tau_{1/2}$ **(k=1) d**	9.913(8)	9.914(6)	9.914(7)
Combined $\tau_{1/2}$ (k=1) d	**9.914(4)**		

Table 3: Uncertainty budget for the half-life measurements of ^{225}Ac.The weighted mean of the final half-life determination was 9.914(4) d. All uncertainties are given at k=1 unless otherwise stated.

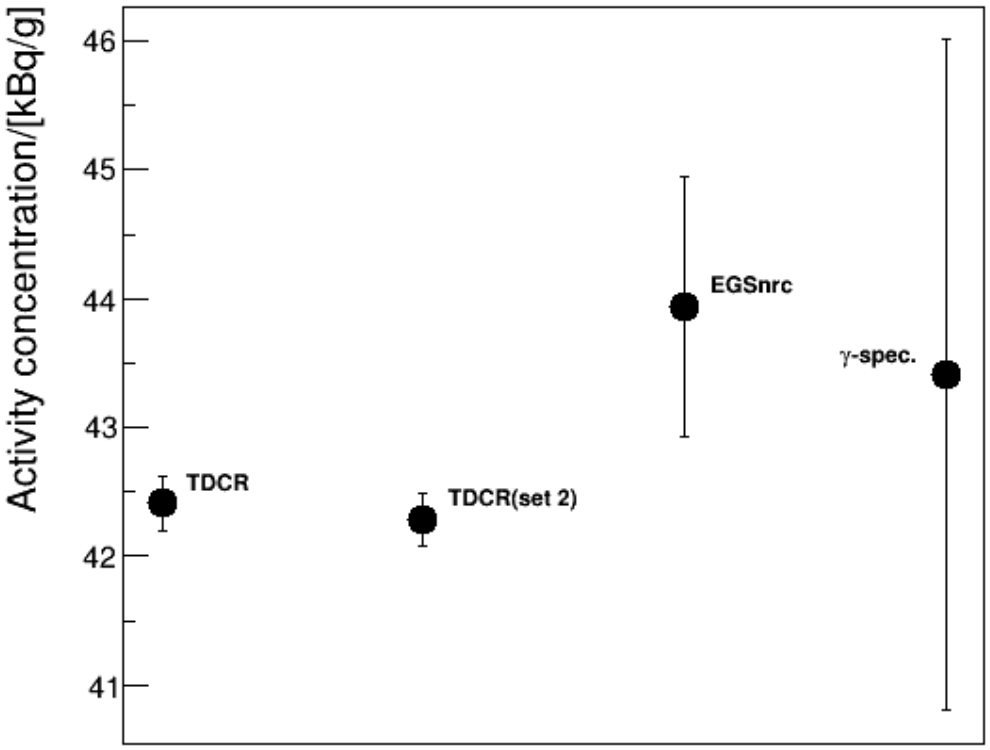

Figure 3: Activity concentration of an ^{225}Ac liquid sample by TDCR and γ spectroscopy. The TDCR point indicates the UltimaGold AB dataset used in the final determination. The TDCR(set 2) point was a redundant measurement set used for comparison. The EGSnrc point represents an IC measurement using a calibration factor determined from an EGSnrc simulation of a Vinten 671 IC. The uncertainties displayed in the figure are the expanded uncertainties at k=2.

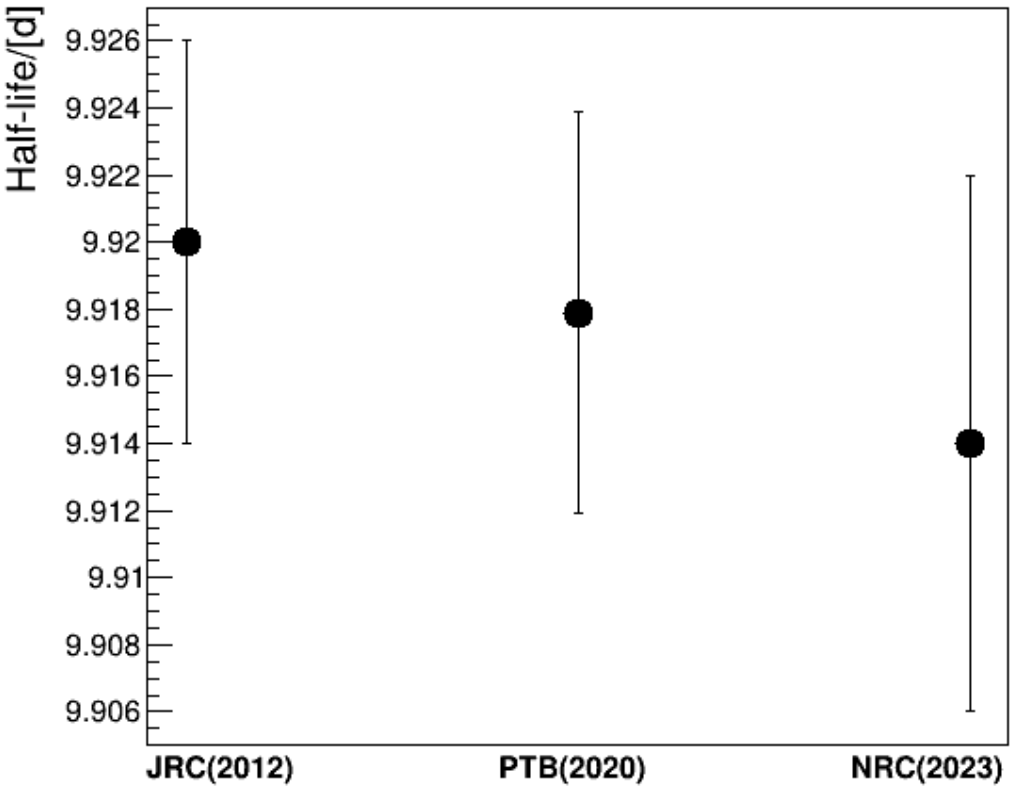

Figure 4: The half-life determined by JRC(**?**]), PTB(**?**]) and NRC(this work). The uncertainties displayed in the figure are the expanded uncertainties at k=2.

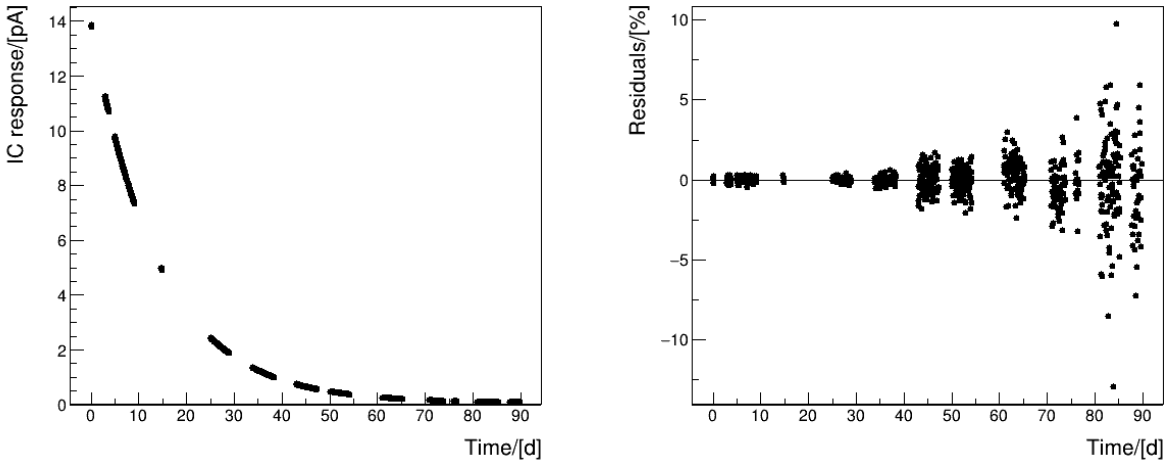

Figure 5: The IC response (left) and the residuals of the half-life fit (right) as a function of days from the first measurement.

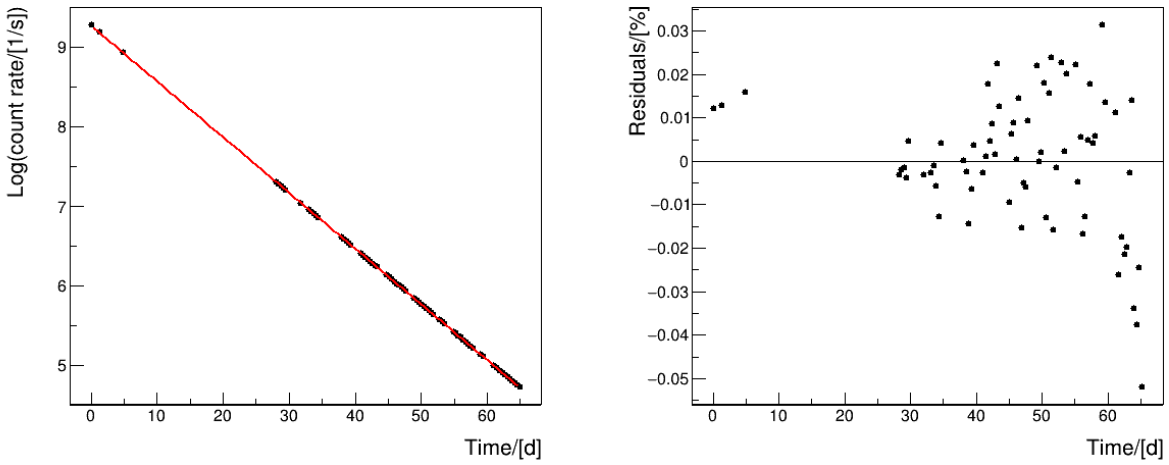

Figure 6: The natural log of the LSC doubles count rate (left) and the residuals of the half-life fit (right) as a function of days from the first measurement. The LSC triples count rate behaviour is identical and not included here for brevity.