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Standardization of radium-223 by liquid scintillation counting

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A B S T R A C T

Liquid scintillation (LS) counting was undertaken as part of the primary standardization of ^{223}Ra. Radium-223 decays with a half life of 11.43 d through a chain of shorter-lived daughter radionuclides, resulting in five alpha decays and three beta decays. The CIEMAT/NIST method of tritium efficiency tracing was employed, with the beta efficiencies being calculated using the program CN2004, developed by the Physikalisch-Technische Bundesanstalt (PTB). The total calculated LS efficiency, considering all daughter radionuclides, was approximately 598%. Separate experiments were performed to rule out loss of the 3.96 s ^{219}Ra daughter from the cocktail and possible counting loss of the 1.78 ms ^{215}Po daughter due to LS counter dead-time. No loss was observed in either experiment. In the final experiment an expanded uncertainty ($k=2$) of 0.55% was achieved. Results were in excellent agreement with confirmatory measurements performed by $2\pi\alpha$ proportional counting. However, results are not in agreement with methods based on gamma ray measurements.

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1. Introduction

Radium-223 decays with a half-life of 11.43 ± 0.05 days (ENSDF, 2006) through a series of daughter radionuclides to stable ^{207}Pb. This series is depicted in Fig. 1. The resulting 5 alpha decays and three beta branches are the reason there is interest in this radionuclide as a radiopharmaceutical. Radium-223 has undergone Phase II clinical trials in Europe to assess the anti-tumor efficacy and the effect on skeletal metastases in late-stage, hormone refractory prostate cancer (Nilsson et al., 2007). Radium-223 is also of interest in environmental measurements where it is used in conjunction with shorter lived ^{224}Ra ($t_{1/2}$=3.66 d) to trace submarine groundwater discharge (Santos et al., 2009) or understand transport processes in marine sediment (Hancock et al., 2000).

The aim of this study was to develop the methods to accurately assay the activity of a solution by absolute methods. That primary standard is then used to develop a secondary method used to routinely assay samples submitted for calibration. The primary methods employed were $4\pi\alpha\beta$ liquid scintillation (LS) counting and $2\pi\alpha$ proportional counting (PC).

These measurements were performed as part of a larger exercise to standardize ^{223}Ra. Experiments 1 and 3–5 (E1, E3, E4, and E5) are in some part discussed here. Comparison of results between experiments was achieved by measurement of a 5 mL ampoule versus a radium (^{226}Ra) reference source on the NIST secondary "4π"-γ ionization chamber. Full details of the overall exercise and the confirmatory measurements by $2\pi\alpha$ proportional counting can be found in Zimmerman et al. (in prep.). In addition, the development of secondary standards is presented in these proceedings by Bergeron et al. (these proceedings).

2. Material and methods

2.1. General

The solutions for all experiments were supplied by Algeta ASA[1] (Oslo, Norway). The proprietary composition was specific to the use as a radiopharmaceutical and could be considered to be ^{223}Ra in a saline solution and a citrate buffer. Additional inactive solution of the same composition was also supplied and was used for all dilutions and carrier additions to LS cocktails. From the received solutions, a 5 mL solution sample in a NIST 5 mL flame-sealed ampoule and a dilution by a factor of nominally 200, were gravimetrically prepared. Liquid scintillation sources were prepared from the dilution of the master. All solutions were determined to be free of gamma-ray-emitting impurities and estimates of activity were made by HPGe spectroscopy measurements of dilution ampoules. The ampoules prepared from the

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[1] Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

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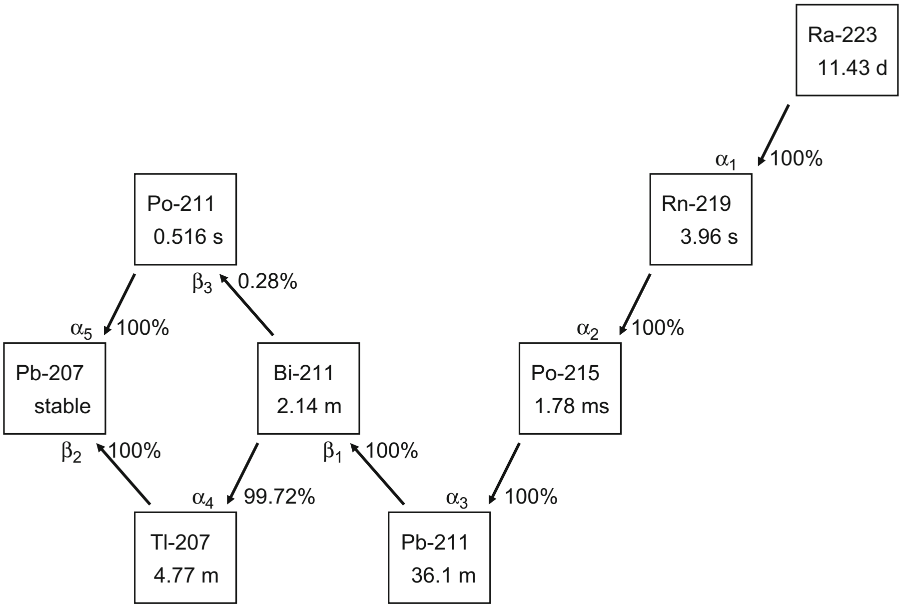

Fig. 1. The decay of ^{223}Ra and daughter radionuclides to stable ^{207}Pb.

Table 1
Composition of liquid scintillation cocktails used in the experiments.

Experiment & composition number	Scintillator	Scintillator volume (mL)	Aqueous component	Aliquot size (mL)	Aqueous fraction, % (vol)	Stable
E1-1	HF	10	0.02 mL H_2O	~0.05	0.8	N
E1-2	OF	10	0.02 mL H_2O	~0.05	0.8	N
E1-3	HSIII	10	0.02 mL H_2O	~0.05	0.8	Y
E1-4	RS	10	0.02 mL H_2O	~0.05	0.8	N
E3-1	HSIII	3,10,22	–	~0.04	1.3,0.4,0.2	Y
E3-2	PCS	3,10,22	–	~0.04	1.3,0.4,0.2	N,Y,Y
E3-3	HSIII	10	1 mL carrier	~0.05	11	Y
E3-4	PCS	10	1 mL carrier	~0.05	11	N
E4-1	UGAB	15	1 mL carrier	~0.05	8	N
E4-2	UGAB	15	1 mL 6 mol L^{-1} HNO_3	~0.05	8	Y
E4-3	HSIII	15	1 mL carrier	~0.05	8	Y
E4-4	HSIII	15	1 mL 6 mol L^{-1} HNO_3	~0.05	8	Y
E5	HSIII	10	0.5 mL carrier	~0.07	6	Y

See text for explanation of scintillator codes and discussion of carrier solution.

high activity solutions were measured on the NIST "4π"-γ IC against a radium (^{226}Ra) reference source. By assigning activity values to this ampoule based on individual measurement methods and determining a *K*-value from each measurement, results were compared across methods and between experiments.

The cocktail compositions of the various LS series are summarized in Table 1, where HF refers to HionicFluor (Packard Biosciences, Inc., Groningen, Netherlands), OF refers to OptiFluor (Packard Biosciences, Inc., Groningen, Netherlands), HSIII refers to Optiphase HiSafe III (Perkin Elmer Life Sciences, Norwalk, CT, USA), RS refers to Ready Safe (Beckman-Coulter, Inc., Fullerton, CA, USA), PCS refers to PCS (GE Healthcare, Buchinghamshire, England), and UGAB refers to Ultima Gold A/B (Packard Biosciences, Inc., Groningen, Netherlands).

All liquid scintillation samples were prepared in standard 22 mL low potassium glass LS vials with foil-lined caps (Wheaton model #986542, Millville, New Jersey, USA). Quenching was varied in all cocktails of E1, E4, and E5 by the addition of between 40 and 240 μL of a 1 to 10 dilution, by volume, of nitromethane in alcohol. No quench agent was added to E3 cocktails used for examining possible ^{219}Rn loss nor to those used in the NIST triple-to-double coincidence ratio (TDCR) LS system. For each composition at least two background samples of identical chemical composition were prepared at the two extremes of the quench range.

2.2. Experiment 1

Experiment 1 was considered preliminary, to find a suitable cocktail composition that resulted in stable cocktails. Cocktails were prepared as noted above. The vials were sequentially counted 5 min each for 10 cycles on the Packard 2500TR LS spectrometer, removed, re-agitated, and counted in the same fashion on the Beckman LS6500 spectrometer counter. Count rates were of the order of 2500 s^{-1}. Results were assessed for the stability of the counting rates.

Preliminary measurements revealed a discrepancy of 5–10% between the LS estimated activities, the Ge measured activities, and those stated by the supplier (also Ge based). Therefore, experiments were designed to look for possible losses of that magnitude.

2.3. Experiment 3

Because the decay chain includes a ^{219}Rn daughter an experiment was designed to look for possible losses into the air space above the cocktail into the LS vial. Being the second member of the decay chain, the loss of radon would have a non-negligible effect on the efficiency if the following daughter radionuclides did not return to the cocktail. Loss of ^{219}Rn was not expected because of the short, 3.98 s half-life. This was confirmed experimentally by preparing three liquid scintillation vials for each of two scintillants in experiment 3. The volume of cocktail was varied from 3 to 22 ml. The change in the volume of the air gap in the top of the vial is presumed to allow more radon to leave the solution in the vial with the smallest volume of scintillator. A background vial was made at each volume. The vials were kept in the dark immediately after being made, to begin dark adapting, and placed in the counter within 30 min of preparation. Vials were sequentially counted in the Packard LS spectrometer 15 min per vial for 4 cycles and, following a weekend power outage, 10 cycles.

In order to investigate the possible loss of counts of the 1.78 ms ^{215}Po daughter due to the coincidence resolving time and the deadtime of the LS counters, one of the cocktails (composition E3-3) was counted in the NIST TDCR (Zimmerman et al., 2003, 2004) using deadtime settings of 24 and 80 ms. No efficiency variation techniques (i.e., gray filters, defocusing, etc.) were applied. Four repeated measurements were taken at each deadtime setting with the source remaining in the sample chamber throughout the experiment. The theoretical magnitude of the effect on the count rate was calculated by integrating the portion of the distribution of time intervals between the decay of ^{219}Rn and the decay of ^{215}Po that would fall within the deadtime setting of the TDCR. The deadtime of the Packard spectrometer is unknown, but predicted to be on the order of 12 μs. The results of the experiment were intended to verify the calculations. From this point forward count rates for all experiments were kept at levels previously determined to have little effect on LS counter deadtime, nominally 1000 cps.

Finally, another two series of samples were prepared to confirm the stability of cocktails prepared with HSIII and to check the stability of those prepared with PCS. These sources were sequentially counted for 10 cycles of 15 min each on the Packard LS spectrometer. The samples were removed from the counter, re-agitated, and counted for 10 cycles of 20 min per sample on the Beckman LS spectrometer.

2.4. Experiments 4 and 5

In E4 and E5 the CIEMAT/NIST ^{3}H-standard efficiency tracing method (Coursey et al., 1986; Zimmerman and Collé, 1997) of LS counting was used as the primary measurement of the activity concentrations of the dilutions. Briefly, this method involves imposing a chemical quench agent to vary the efficiency of a set of tritium LS cocktails compositionally matched to a set of ^{223}Ra LS cocktails. A calculational model is used to translate the change in tritium efficiency to a change in efficiency for the beta branches in the decay of ^{223}Ra and its daughters. LS alpha efficiencies are taken as 100%. In most cases, decay and atomic data provided with CN2004 were used for the calculations. The decay data are in agreement with those listed in ENSDF (2006).

In Experiment 4, LS sources were prepared in two types of scintillant: UGAB and HSIII. Ten ^{223}Ra sources and four background sources were prepared for each scintillant. The cocktails contained 15 mL of scintillant, nominally 44 mg aliquots of active solution and between 2 and 14 drops of a 1 to 10 dilution (by volume) of nitromethane in alcohol, as a quenching agent. Five samples for each scintillant also contained nominally 1 mL of inactive carrier solution, with the remaining five for each scintillant containing nominally 1 mL of 6 mol L^{-1} nitric acid. After discussions of preliminary results, the addition of nitric acid was used at the suggestion of PTB, as it had been used successfully in the measurement of ^{227}Ac, a parent of ^{223}Ra (Kossert, 2007). Background sources were prepared in a similar manner, substituting carrier for the active component. Samples were sequentially counted 10 min each for 10 cycles on the Packard spectrometer.

Counting sources for Experiment 5 were prepared in a similar manner, using HSIII as the scintillant. Five ^{223}Ra sources and two background sources were prepared. The cocktails contained 10 mL of scintillant, nominally 71 mg aliquots of active solution, nominally 500 μL inactive carrier solution, nominally 100 μL distilled water, and between 2 and 14 drops of diluted nitromethane, as a quenching agent. A set of five sources with similar composition was prepared using a dilution of a NIST tritium standard reference material 4927F (NIST, 2000) and inactive carrier. Samples were sequentially counted 15 min each for 10 cycles on a Packard spectrometer. Samples were then removed from the counter, agitated and sequentially counted 20 min each for 10 cycles on a Wallac Guardian 1414 LS spectrometer, modified to disable the anticoincidence shield.

The efficiency tracing code CN2004 (Günther, 2004) was utilized in the analysis of the beta branch efficiency tracing. The transitions considered in activity determinations are listed in Table 2, where Nr Pro is the program code for the degree of forbiddenness. A *kB* value of 0.012 g MeV^{-1} cm^{-2} was used in the calculation. Given the high beta energy and number of alpha particles, the choice of *kB* does not have a large impact on the

Table 2
Listing of principal radiations considered in activity determinations conducted in this study.

E_α (keV)	I_α	Nuclide	Nr Pro
5433.6(5)	0.0222(20)	^{223}Ra	
5501.6(10)	0.0100(15)	^{223}Ra	
5539.80(90)	0.090(2)	^{223}Ra	
5606.73(30)	0.252(5)	^{223}Ra	
5716.23(29)	0.516(13)	^{223}Ra	
5747.0(4)	0.090(20)	^{223}Ra	
5871.3(10)	0.010(2)	^{223}Ra	
6278.2(7)	0.1623(14)	^{211}Bi	
6425.0(10)	0.075(6)	^{219}Rn	
6552.6(10)	0.129(6)	^{219}Rn	
6622.9(6)	0.8377(14)	^{211}Bi	
6819.1(3)	0.794(10)	^{219}Rn	
7386.2(8)	1	^{215}Po	
E_β (keV)	**I_β**	**Nuclide**	
18.564(3)	1	^{3}H	0
534	0.00268(9)	^{207}Tl	1
535(6)	0.0632(10)	^{211}Pb	0
574(5)	1	^{211}Bi	0
962(6)	0.0154(8)	^{211}Pb	1
1367(6)	0.9130(12)	^{211}Pb	0
1436(6)	0.99732(9)	^{207}Tl	0
E_γ (keV)	**I_γ**	**Nuclide**	
328.10(12)	0.0000140(14)	^{207}Tl	
404.853(10)	0.0378(5)	^{211}Pb	
427.088(10)	0.0176(4)	^{211}Pb	
569.62(12)	0.0000159(20)	^{207}Tl	
832.01(3)	0.0352(5)	^{211}Pb	
897.77(12)	0.00260(9)	^{207}Tl	

Data were obtained from ENSDF (2006). Uncertainties are given as standard (k=1) uncertainties. Absolute intensities are given as fractional values per decay of the respective radionuclide. Nr Pro is the CN2004 code for the degree of forbiddenness.

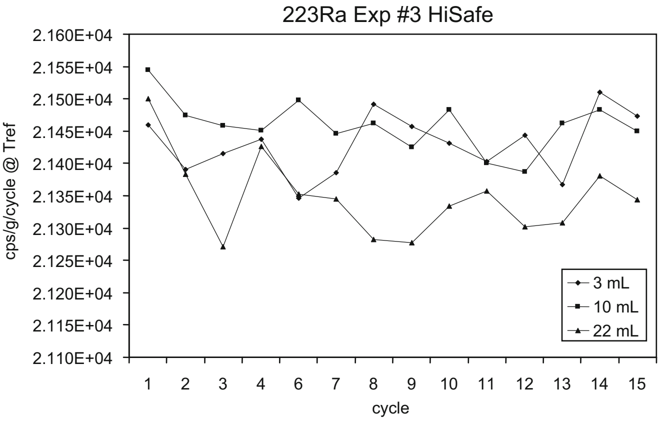

Fig. 2. Decay corrected count rates as a function of measurement time for LS vials containing 3, 10 and 22 mL of LS cocktail.

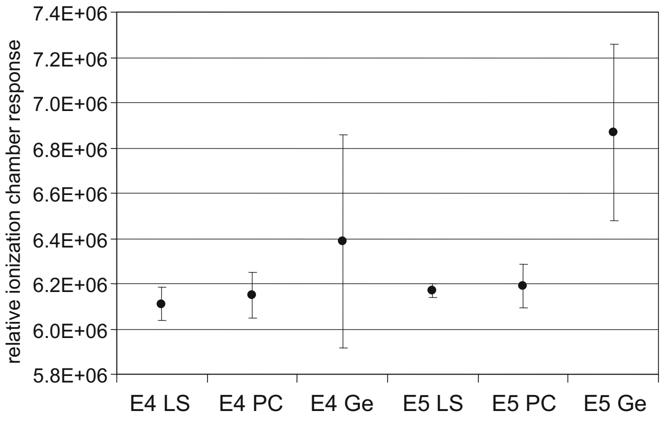

Fig. 3. Results of activity determinations by the CIEMAT/NIST method of ^{3}H efficiency tracing liquid scintillation counting (LS), $2\pi\alpha$ proportional counting (PC), and germanium spectroscopy (Ge) expressed relative to measurements of a radium (^{226}Ra) reference source on the NIST 4π–γ secondary ionization chamber. Uncertainty bars represent expanded uncertainties, k=2.

results. Over a range of 0.005–0.012 g MeV^{-1} cm^{-2} the resulting calculated efficiency changes by 0.01%. Due to the relationship of half-lives in the decay chain, equilibrium factors were calculated using Mathematica. Tritium samples from E5 were used in the tracing of both E4 and E5. The effect due to the difference in cocktail volume and the degree of quenching was calculated by comparing the tracing results for the two volumes and the difference was added as a component of uncertainty in E4. The average calculated ^{223}Ra LS efficiency was 599% in E5, for both LS spectrometers, covering a range of 598.7–599.0%, corresponding to a ^{3}H LS efficiency of 28.1–34.3% and a figure of merit range of 2.1–1.7. In E4 the average ^{223}Ra LS efficiency was 596%, covering a range of 594.2–597.2%, corresponding to a ^{3}H LS efficiency of 19.8–38.8% and a figure of merit range of 2.95–1.50.

Additionally in E4 and E5 $2\pi\alpha$ proportional measurements were made on sources prepared from the same solutions used to prepare the LS samples. Details of these measurements are presented elsewhere.

3. Results and discussion

Those compositions that resulted in stable cocktails are noted in Table 1. Cocktails were considered unstable if the efficiency-traced activity showed a discernable trend and changed by more than 0.5% over 10 cycles. The measurements from unstable cocktails were not included in the activity determinations.

3.1. Experiment 3

Fig. 2 shows decay-corrected massic count rates for the three E3-1 sources as a function of time. If there were a loss of radon to the air space above the vial a lower count rate should be observed in the vial with the lowest volume of scintillant. Instead, a lower count rate was observed in the vial containing 22 mL of scintillant. This was considered to be a loss of light collection in this sample due to the fact that the meniscus was not visible to the phototubes, being in the neck of the vial rather than the body. It has previously been shown that a larger fraction of the light produced in the cocktail exits the vial at the meniscus (Durán Ramiro and García-Toraño, 2005).

Assuming a deadtime of 50 μs, the calculated counting loss of a radionuclide having a 1.78 ms half-life is 1.93%. From the TDCR experimental data, a difference in the average counting rates in the logical sum of doubles counting channel of 1.4% was observed between the two deadtime settings, which is consistent with the calculated value. Because of this, combined with the fact that the magnitude of the suspected effect was 5–10%, it was concluded that losses due to the Po-215 half-life and instrument resolving time were not the cause of the observed discrepancy. Given the consistency of the data and calculation, the theoretical loss was calculated for a deadtime value of 12 μs.

The theoretical loss is 0.47% of the ^{215}Po. As a fraction of the overall uncertainty, the effect is 0.47/599=0.08%. Because the deadtime was estimated, no correction was made to the activity and the effect was included as a component of the uncertainty.

3.2. Experiments 4 and 5

Results of activity determinations can be found in Fig. 3. Uncertainty bars represent expanded, k=2, uncertainties on the individual determinations. It can be seen that there is good agreement between the LS and PC activity determinations, being less than 0.2% in both experiments. While the gamma-ray spectrometry based activity determinations cannot be said to disagree in both cases, the uncertainties overlap in one instance, there remains a difference of nominally 4% and 12% in experiments E4 and E5, respectively. Further experiments are planned to investigate these possible differences and measure gamma probabilities based on the LS and PC data.

The associated evaluated components of uncertainty on the LS measurements can be found in Table 3. The uncertainty analysis methodology and nomenclature used for the reported uncertainties are based on uniform NIST guidelines and are compatible with those adopted by the principal international metrology standardization bodies (Taylor and Kuyatt, 1996; ISO Guide, 1995). The combined standard uncertainty is the quadratic combination of the standard deviations (or standard deviations of the mean where appropriate), or approximations thereof, for the component uncertainties. For discussion of uncertainties on PC and gamma-ray spectrometry measurements see Zimmerman et al. (in prep).

Using two different techniques for assaying the solutions—LS counting, which detects all radiations emitted in the ^{223}Ra decay chain with differing degrees of efficiency, and proportional counting, which was performed in a manner to detect alpha particles only—agreement to better than 0.2% was achieved for the two methods with both master solutions. Moreover, this was achieved with an expanded uncertainty (k=2) of the order of only 1.1%. These results give us confidence in the LS results and in the determination that no large effects are being observed from either

Table 3
Components of uncertainty in E4 and E5 activity determinations.

Component, u_i	Comment	Evaluation type	%, E4A1	%, E5A1
LS Measurement precision E4	Standard deviation for n=15 determinations (equivalent to standard deviation of the mean) as obtained with 3 different cocktail compositions (5 sources each composition) measured 10 times (150 determinations in all). Passes normality test at 95% and 99%. The typical internal relative standard deviation of the mean (n=10 cycles) for each determination ranged from 0.02% to 0.09%.	A	0.08	–
LS Measurement precision E5	Standard deviation for n=10 determinations (equivalent to standard deviation of the mean) as obtained with 5 sources measured 10 times in 2 different LS counters (150 determinations in all). Passes normality test at 95% and 99%. The typical internal relative standard deviation of the mean (n=10 cycles) for each determination ranged from 0.02% to 0.05%.	A	–	0.16
Counting losses	Estimated counting loss of 1.78 ms decay of ^{218}Po due to an assumed 12 µs counter deadtime	B	0.08	0.08
Gravimetric determinations for LS cocktails	Estimated standard uncertainty on the determination of ^{223}Ra mass for a single cocktail	B	0.05	0.05
Dilution factor	Estimated standard uncertainty on the gravimetric determination of the dilution factor	B	0.18	0.07
^{223}Ra decay corrections	For a standard uncertainty of decay corrections over: E4-16 hours, and E5-5 days	B	0.002	0.01
^{223}Ra efficiency calculations	Step size in CN2004 calculations	B	0.02	0.02
Cocktail volume	Estimated uncertainty due to difference in cocktail volume between ^{3}H and ^{223}Ra	B	0.45	–
Livetime	Estimated uncertainty in the correction to the LS counting interval	B	0.05	0.05
Background	Estimated uncertainty due to an average 5% uncertainty in background determination	B	0.003	0.001
Activity of ^{3}H standard	Estimated uncertainty due to 0.72% (k=2) uncertainty in ^{3}H standard activity	B	0.001	0.001
Branching ratios	Estimated uncertainty due to uncertainty in branching ratios	B	0.18	0.18
Combined ($u_c=\sqrt{\sum u_i^2}$)			0.54	0.27
Expanded (U_c=$u_c k$; k=2)			1.07	0.55

loss of ^{219}Rn from solution or loss of counts from the ^{215}Po decay due to counter deadtime. Loss of radon has been avoided in the solid PC sources and count rates were very low in the PC system so it would not suffer from the same potential type of losses due to counter deadtime as the LS system.

4. Conclusions

Liquid scintillation (LS) counting was undertaken as part of the primary standardization of the alpha-emitting medical radionuclide ^{223}Ra. Radium-223 decays with a half life of 11.43 d though a chain of shorter-lived daughter radionuclides, resulting in the emission of five alpha particles and three high energy beta emissions. The CIEMAT/NIST method of tritium efficiency tracing was employed, with the beta efficiencies being calculated using the program CN2004, developed by the Physikalisch-Technische Bundesanstalt (PTB). The total calculated LS efficiency, considering all daughter radionuclides, was approximately 599%. Cocktails were prepared using the commercial liquid scintillants Hionic-Fluor, Opti-Fluor, Opti-Phase HiSafe III, Ready Safe, and Ultima Gold AB, with an additional aqueous fraction of either a carrier solution or, for some cocktails, 6 mol L^{-1} nitric acid. Not all compositions resulted in stable cocktails. Only HSIII consistently resulted in stable cocktails, while UGAB resulted in stable cocktails with the addition of nitric acid, but not with the addition of the identical amount of carrier solution. Separate experiments were performed to rule out loss of the 3.96 s ^{219}Ra daughter from the cocktail and possible counting loss of the 1.78 ms ^{215}Po daughter due to LS counter dead-time. No loss was observed in either experiment. In the final experiment an expanded uncertainty (k=2) of 0.5% was achieved. Results were in excellent agreement with confirmatory measurements performed by 2$\pi\alpha$ proportional counting.

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