Activity measurement of phosphorus-32 in the presence of pure beta-emitting impurities

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We describe the activity measurements undertaken at the CSIR's National Metrology Laboratory on a solution of the pure beta-emitting radionuclide phosphorus-32 that formed part of an international key comparison. Depending on the production mode, the pure beta-emitters ^{33}P and ^{35}S are possible impurities. Since exploratory source measurements indicated the presence of radioactive contaminants, the occurrence of both ^{33}P and ^{35}S was assumed. The method adopted to extract the ^{32}P activity accurately was thus to follow the decay over an extended period of time, taking advantage of the different decay rates. The extracted counting rates were converted to activities by comparison/computation against ^{63}Ni sources of known activity. The ^{32}P activity was also independently given by the Triple-to-Double Coincidence Ratio efficiency calculation technique, after first correcting the double and triple count rates for the impurity contributions.

Introduction

Phosphorus-32 is an important radionuclide used in life-science laboratories as a radiolabelled DNA probe and in nuclear medicine as a therapeutic isotope. Applications include the treatment of cancer-induced bone pain and infusional brachytherapy for the treatment of various cancers. Here the calculated dose is achieved by delivering known amounts of activity. Activity measurements are ultimately traceable to national radioactivity measurement standards, offering the highest level of accuracy achievable. The Mutual Recognition Arrangement (MRA) requires that measurements carried out at national metrology institutes are checked regularly for uniformity and equivalence purposes.[1] With this as an objective, an international key comparison of ^{32}P activity measurements was organized by the International Bureau of Weights and Measures (BIPM), in Paris, France, with a comparison reference time of 01 February 2005, 00:00 UTC. A similar comparison exercise conducted in 2002 led to a number of publications[2–4] highlighting the challenges and difficulties encountered due to contaminants.

Aliquots of the master solution in flame-sealed glass ampoules were sent to each of the 10 participating national laboratories, with measurements taking place during the first half of 2005. Depending on the production mode, the pure beta-emitting radionuclides ^{33}P and ^{35}S are possible impurities. Preliminary measurements made at the CSIR's National Metrology Laboratory did indeed indicate the presence of radioactive impurities, thereby precluding the use of standard counting techniques to measure the ^{32}P activity. The activity was determined instead by following the decay over an extended time.

Indication of radioactive impurities

Two powerful methods based on liquid scintillation counting (LSC) are generally used for the measurement of pure beta-emitting radionuclides. The one, the CIEMAT/NIST method,[5] uses an external standard of known activity to trace the counting efficiency; the other is more direct, namely the triple-to-double coincidence ratio (TDCR) technique.[6,7] Both methods are founded on the same underlying physics principles to calculate the source efficiencies as a function of the figure-of-merit,[8] P, that characterizes LSC detection systems. At the CSIR NML, a counting system suitable for both methods is available and appropriate source measurements were acquired for the application of both methods. Exploratory data analyses, made on the assumption that only ^{32}P was present, gave a source activity value from the absolute TDCR technique that was 1.8% higher than that obtained by the CIEMAT/NIST tracer method. This inconsistency is indicative of the presence of impurities because each method responds differently from these. Another indicator was the unrealistically low value extracted from the TDCR analysis for the figure-of-merit ($P = 0.027$ e keV^{-1}).

Methods

Assuming that both ^{33}P and ^{35}S were present, and since they could not be determined independently, the method adopted to extract the ^{32}P activity in this metrology exercise was to follow the decay over an extended time, taking advantage of the different decay rates of the radionuclides (the half-lives of ^{32}P, ^{33}P and ^{35}S are $T_{\frac{1}{2}} = 14.284$ days, 25.383 days and 87.32 days, respectively[9]).

Approach

Although this is a well-established technique,[10] a few variations were incorporated for the liquid scintillation measurements presented here: sets of both double- and triple-coincidence data were collected and analysed separately; fresh counting sources were prepared on a weekly basis to avoid possible loss of counts from adsorption to the glass counting vials, requiring the rates per unit mass to be analysed; and two independent methods were used to determine the activity subsequently: (i) by the use of a variant of the CIEMAT/NIST method whereby ^{63}Ni sources were preferred to the usual tritium standard, the former being considered to provide a more reliable indicator of the efficiency, and (ii) by a novel application of the TDCR efficiency calculation technique whereby the double- and triple-coincidence count rates were first corrected for the impurity contributions determined by the decay monitoring method described below.

Description

For a given source comprising mass m of the master solution, the disintegration rates of ^{32}P, ^{33}P and ^{35}S are A_1, A_2 and A_3, respectively, at some selected reference date. Then at a time t after the reference date, the measured source count rate per unit mass of the master solution is given by:

$$C(t) = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t},$$

where the λ_i terms are the respective decay constants given by $\ln 2/T_{\frac{1}{2}}$ and $C_i = \dfrac{A_i \varepsilon_i}{m}$, the ε_i being the respective beta detection efficiencies of each radionuclide.

Since the radioactive decay of the solution is being followed, it is a necessary requirement that the counting efficiency remain unchanged for each source prepared. Although unlikely in practice, any efficiency variation is minimized by duplicating the source preparation and counting conditions as closely as possible.

Experimental

The decay was followed over 44 days, by observing 12 different liquid scintillation counting sources. The sources were prepared

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in commercial glass vials, which were pretreated with a solution comprising 4.5 g NaH_2PO_4 in 100 ml H_2O. Accurately weighed aliquots of the radioactive material were dissolved in 12 ml liquid scintillator (Quicksafe A from Zinsser Analytic), to which 3 ml per litre of 3 M HCl had been added to minimize adsorption. Initially, a dilution (4.7973 times weaker) prepared from the ^{32}P master solution was used and, when this became too weak, aliquots were drawn directly from the master solution. A quenching agent comprising 0.5 ml chloroform was added to the sources to reduce the production of spurious pulses from phototube afterpulsing.

The sources were counted with a detection system comprising three high-gain phototubes connected in coincidence through a specially manufactured double- and triple-coincidence electronic module, using conventional analogue signal processing. The electronic threshold of each phototube pulse train was set below the pulse-height spectrum single-electron peak. The contribution from afterpulsing was monitored and recorded simultaneously with the measured counting data.

Measurements began on 9 March 2005 and six sources were counted during the first week of measurements, with six sets of measurements being recorded for each source. Thereafter, fresh sources were prepared on a weekly basis, with counting taking place the next day and again a week later. Each counting set comprised three singles counts, three double-coincidence counts and a triple-coincidence count, the counts being recorded simultaneously during a 300-second counting interval. The double-coincidence count rates were typically 1500 s^{-1}, with the corresponding background rate being 2 s^{-1}. In total, 106 sets of measurements were made on the 12 ^{32}P sources.

Data analysis

The recorded data were corrected for background, deadtime (1.0 μs), coincidence resolving time (0.47 μs) and afterpulsing. The corrected data from each source were converted to count rate per unit mass of the master solution. Figure 1 shows a typical set of such data (those collected on day 1). These count rate concentrations, C_i, were analysed as a function of the time interval, t_i, from a locally defined reference time (close to the measurement start date) by fitting the data points with a mathematical expression comprising the sum of three exponential decay functions. A weighted least-squares fitting procedure was applied, whereby

$$Q = \sum_i w_i [C_i - C_1 \exp(-\lambda_1 t_i) - C_2 \exp(-\lambda_2 t_i) - C_3 \exp(-\lambda_3 t_i)]^2$$

was minimized by differentiating with respect to the coefficients C_1, C_2 and C_3 and equating to zero. This gives rise to a set of linear algebraic equations that can be expressed in matrix form, the coefficient solutions and uncertainties being extracted by a matrix inversion technique. Each datum point was weighted as $w_i = 1/\sigma_i^2$ according to the standard deviation given by the source counting statistics (σ_i). The practical realization of the fitting was through a locally written Fortran computer program. Tests on simulated data with built-in statistical variation indicated that the coefficients were correctly extracted, the fluctuations being consistent with the calculated standard uncertainties.

Results from the decay fit

All the double-coincidence data are shown in Fig. 2, together with plots of the curves best describing the measured decay. An excellent fit was found, with a reduced chi-square value of 1.28 and an R^2 value of 0.9999889. The three extracted coefficients provided the count rate concentrations of the master solution at the local reference date ($C_1 = 93\,970 \pm 173$ s^{-1} g^{-1}, $C_2 = 2355 \pm$
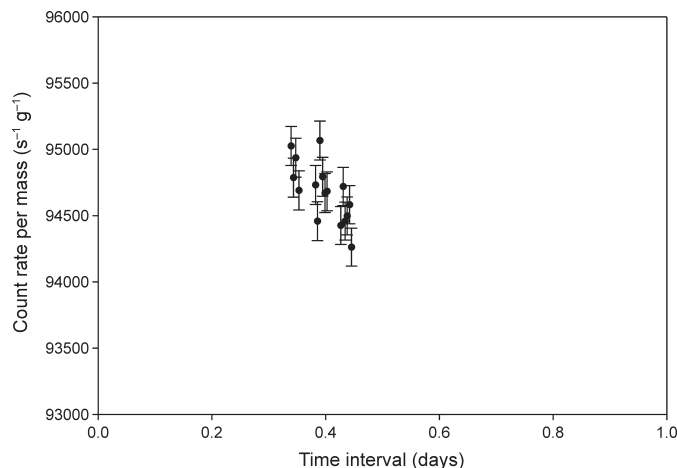
Fig. 1. Graph showing the cluster of data points collected on day 1 plotted against the time interval (days from the local reference date). These corrected double-coincidence data are expressed as the count rate concentration given by the master solution.
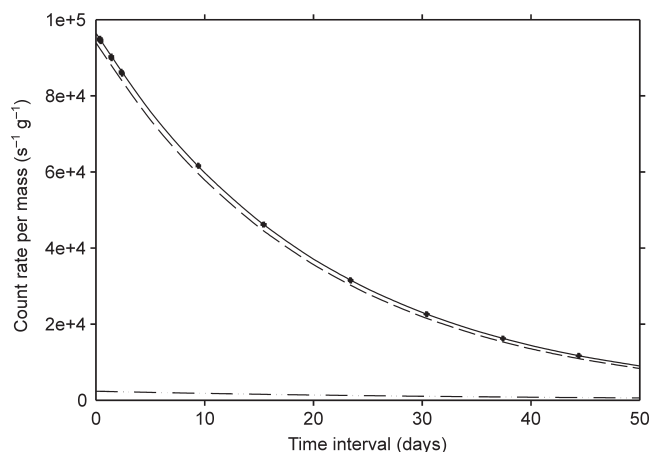
Fig. 2. Graph of the clusters of 106 data points collected in total plotted against the number of days from the local reference date. The count rate is that given per gram of the master solution received. The continuous curve is the best least-squares fit to the data of the sum of three exponential decay functions (for ^{32}P, ^{33}P and ^{35}S). The broken lines show the extracted exponential decay curves for ^{32}P (dashes) and ^{33}P (dash–dots).

231 s^{-1} g^{-1} and $C_3 = 134 \pm 75$ s^{-1} g^{-1}). The standard uncertainties shown were given by the diagonal elements of the inverse matrix. The off-diagonal elements provided the covariances between the coefficients, from which the following correlation coefficients were derived: $r(C_1,C_2) = -0.9875$, $r(C_1,C_3) = +0.9627$, $r(C_2,C_3) = -0.9921$. In the same way, a data set comprising the triple-coincidence data that were collected simultaneously with the double-coincidence measurements, was independently analysed. The fit was slightly poorer than for the double-coincidence set, with a reduced chi-square of 1.38. The results obtained from this fit gave the coefficients as follows: $C_1 = 93\,862 \pm 172$ s^{-1} g^{-1}, $C_2 = 1708 \pm 230$ s^{-1} g^{-1} and $C_3 = 311 \pm 75$ s^{-1} g^{-1}.

Table 1. Double- and triple-phototube counting efficiencies ε_i derived from ^{63}Ni activity standards.

Radionuclide	Double-tube efficiency[a] (%)	Triple-tube efficiency[a] (%)
^{32}P	99.39 ± 0.003	99.26 ± 0.004
^{33}P	84.62 ± 0.07	81.62 ± 0.08
^{35}S	75.16 ± 0.10	70.55 ± 0.12

[a]Based on a value for the Birks constant[12] of kB = 0.0100 g/(cm² MeV).

Table 2. Activity results determined from efficiencies obtained by tracing with ^{63}Ni sources. The activity concentrations are specified at the local reference date.

Radionuclide	Double-tube data analysis		Triple-tube data analysis	
	Activity concentration (Bq g^{-1})	Fraction of ^{32}P (%)	Activity concentration (Bq g^{-1})	Fraction of ^{32}P (%)
^{32}P	94 547 ± 174		94 562 ± 173	
^{33}P	2783 ± 273	2.94 ± 0.29	2093 ± 282	2.21 ± 0.30
^{35}S	179 ± 100	0.19 ± 0.11	441 ± 106	0.47 ± 0.11

Counting efficiency determination

To convert the extracted count rates to activity, the required counting efficiencies were determined by two independent approaches. The data analysis in both cases used various modified versions of the computer program[11] EFFY 2 to extract the figure-of-merit P and hence derive the counting efficiencies.

External nickel-63 standards

The extracted solution counting rate per unit mass of each radionuclide was converted to activity concentration by using counting efficiencies derived from external ^{63}Ni tracer measurements. This was achieved by preparing two ^{63}Ni standards of known activity (1836 Bq and 3108 Bq) in the same scintillation/chloroform cocktail used for the phosphorus sources so as to provide comparable quenched states. The ^{63}Ni activities were checked by measuring each source by the TDCR method before 0.5 ml chloroform was added. Three sets of data from a ^{63}Ni source were recorded on each occasion that phosphorus sources were counted.

The ^{63}Ni sources were counted on 10 occasions and the figure-of-merit extracted through a TDCR analysis of the data. In all cases the measured activities of the quenched standards agreed with the known value to within the counting statistics uncertainties. The mean figure-of-merit value of $P = 0.09535 \pm 0.00050$ e keV^{-1} (corresponding to a double-tube efficiency of 42.52%) was used to obtain the efficiencies of ^{32}P, ^{33}P and ^{35}S (Table 1). The resultant activity concentration values (given by $A_i = C_i/\varepsilon_i$), specified on the local reference date, are given in Table 2. The activities determined from the double-coincidence data were decay corrected to the comparison reference time and reported to the BIPM in June 2005, together with the uncertainty budget (Table 3). It is evident that both the ^{33}P and ^{35}S activity ratios given by the triple-coincidence analysis agree with those stated for the comparison result within the uncertainties given by the fits.

TDCR analysis

A conceptually simpler application of the TDCR technique[6,7] was used than the iterative approach previously described[3] to unfold the mixture efficiencies. Here the source counts due to

Table 3. Uncertainty budget for ^{32}P at 1σ, in percentage of the activity concentration.

Uncertainty component	Relative standard uncertainty (%)
Counting statistics and fit to the decay data sets	0.18
Weighing	0.02
Dead time	0.01
Coincidence resolving time	0.005
Satellite pulses	0.015
Background	0.01
Adsorption to the counting vials	0.10
Tracer	0.006
Half life (14.284 ± 0.036 days)	0.18
Combined uncertainty (in quadrature)	0.28

the ^{33}P and ^{35}S impurities were first subtracted from the raw double and triple counts before the data were analysed further. This was achieved by decay correcting each impurity concentration rate (as given by the two fits) to the time of the source measurement and then obtaining the total number of counts due to the impurities by taking into account the source mass and counting interval. Samples of counting sets from all 12 sources were processed in this way. Table 4 shows some of the resultant source data sets (expressed in terms of rates) and the output obtained from a TDCR analysis. The analysis of 25 such sets produced a mean ^{32}P activity concentration of the master solution of 94 490 Bq g^{-1} on the local reference date, with a statistical uncertainty of 44 Bq g^{-1}. The TDCR analysis also demonstrated that the requirement for consistent counting efficiencies over the entire measurement period was met. The mean double-tube efficiency, ε_d, extracted from the analysis was 0.9951 ± 0.0004, in close agreement with that obtained from the ^{63}Ni standards.

Conclusions

This work has shown that an appraisal of a ^{32}P solution by both the TDCR and CIEMAT/NIST methods that leads to an inconsistent activity value is an indicator of the presence of one or more radioactive impurities.

The application of the decay method as described, whereby both double- and triple-coincidence events were followed so as

Table 4. Activity concentration of the ^{32}P master solution extracted from a TDCR analysis of the double- and triple-coincidence data. A number of representative source data sets are shown. The uncertainty shown is due to counting statistics only (1σ).

Source	Solution mass (mg)	Time interval (day)	Double rates (s^{-1})			Triple rates (s^{-1})			TDCR	Extracted from data analysis	
			Total[a]	^{33}P + ^{35}S	^{32}P	Total[a]	^{33}P + ^{35}S	^{32}P		ε_d (%)	^{32}P activity concentration (Bq g^{-1})
1	70.148[b]	0.34757	1387	36.1	1351.7	1378	29.3	1350.1	0.9988	99.43	94 549 ± 149
4	77.162[b]	1.43993	1446	38.5	1408.6	1437	31.4	1407.2	0.9990	99.51	94 375 ± 146
7	87.425[b]	9.42257	1123	35.4	1087.7	1116	29.3	1087.3	0.9996	99.79	94 484 ± 166
9	102.204[c]	23.39063	3219	138.5	3091.3	3193	118.6	3083.3	0.9974	98.87	95 185 ± 99
10	90.383[c]	30.37674	2045	102.4	1946.1	2031	89.5	1944.2	0.9990	99.51	94 488 ± 124
12	78.336[c]	44.36007	918	62.3	854.56	911	57.0	853.32	0.9986	99.32	94 538 ± 187

[a]Uncorrected raw data as measured.
[b]Prepared from the dilution (factor 4.7973).
[c]Prepared from the master solution.

to extract the ^{32}P content in the presence of pure beta-emitting impurities, gave comparable results and provided an internal consistency check. The two schemes adopted to obtain counting efficiencies and thereby convert count rates to activities produced values that agreed to within the specified standard uncertainties.

Participation in this key comparison has advanced the CSIR NML's measurement capabilities, will establish degrees of equivalence with other participating national laboratories and offer traceability for the local user community.

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