Determination of a calibration factor for the nondestructive assay of Guidant ^{32}P brachytherapy sources

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Abstract

A calibration factor ('dial setting') for the nondestructive assay of Guidant TiNi-encapsulated ^{32}P intravascular brachytherapy wire sources has been determined for measurements with the Capintec CRC-12 (sic. 'dose calibrator') ionization chamber. The calibration factor was derived from ionization current measurements with the CRC-12 followed by very quantitative, destructive assays of the ^{32}P content in two sources. Published by Elsevier Science Ltd.

1. Introduction

The use of so-called 'magic bullets' in the treatment of heart disease — i.e. for the reduction of restenosis following balloon angioplasty, by the temporal insertion of high-energy, β-emitting sealed sources into coronary arteries — has been receiving a very high level of interest by the radiation oncology and cardiology communities. The potential benefits of such treatments may be profound in terms of both human and financial healthcare costs (CIRMS, 1998).

The development and use of a TiNi-encapsulated ^{32}P source for such treatments has been under intensive investigation by the Guidant Vascular Intervention, Inc. (Houston, TX), formerly the NeoCardia Corp. As part of a larger collaborative effort between Guidant and the National Institute of Standards and Technology (NIST), Collé (1999) recently reported on the methodology used for the chemical digestion and radionuclidic assay of these sources (hereafter called 'seeds'). Inasmuch as ^{32}P is a pure $β^-$ emitter (with maximum β-spectrum endpoint energy of $E_{\beta(max)} = 1710.6 \pm 0.6$ keV) with no distinct radiative signature (e.g. γ-rays), the ^{32}P content of a given seed could be determined only by very quantitative, destructive assay techniques. These destructive assays served as the necessary link that could unequivocally relate radiochromic-film dosimetry measurements for the seed's absorbed dose spatial distribution (Soares, 1997) to theoretical dose modelling by Monte Carlo calculations (Seltzer, 1997). The assays, at the same time, were used to establish the requisite calibration factors for subsequent nondestructive measurements of the seeds, e.g. for in-house quality control by the manufacturer.

The Capintec CRC-12 'dose calibrator' (a re-entrant ionization chamber) has often served as an ad hoc 'standard' for measuring the activity of various radionuclides after the determination of suitable 'dial setting' calibration factors (Coursey et al., 1998). This paper reports on the determination of this instrument's calibration factor for the nondestructive assay of the ^{32}P content in the Guidant seeds.

2. Experimental aspects

The seeds, to the extent that their proprietary composition can be disclosed, consist of a ^{32}P-containing source material that is encapsulated in a thin-cladded, tubular jacket (0.457 mm o.d.) of a TiNi alloy, whose ends have inserted TiNi wires. One end of the tube is sealed by a hemispherical weld of a TiNi wire plug (of nominal 1 mm length) to the TiNi tube. The other end

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is a long multimeter wire that can be inserted into suitable artery catheters. The ^{32}P-containing 'active' portion of the wire has an internal source length of nominally 27 mm, which is located roughly 1 mm from the end of the wire.

The ionization current measurements with the Capintec CRC-12 dose calibrator were made, in all cases, with the acrylic chamber-well insert (the liner supplied with the instrument) removed and employed Capintec's linear brachytherapy-source holder. The active seed portions of the TiNi wires were inserted inside a 1.00 mm i.d. (French 3) × 1.67 mm o.d (French 5) teflon catheter tube which was placed above a thin-rodded spacer in the source holder. Initially, in order to determine the spacer height H that would give a maximum (or optimal) ionization current, measurements were made with spacers ranging in length from $H = 5$–95 mm. All subsequent measurements to determine the dial setting calibration factor were made at an optimal spacer length of $H = 55$ mm (see below).

The calibration factor determination was based on measurements performed with two seeds, identified as P-97-15-2 and P-97-23-6. The first was measured with the CRC-12 in mid-March 1997, was returned to Guidant for additional comparative evaluations with the previously-performed NIST dosimetry (Soares, 1997) and was then remeasured with the CRC-12 in the latter part of June 1997. The second seed was measured with the CRC-12 in July 1997.

Following the ionization current measurements with the CRC-12 dose calibrator, the active portions of both seeds were cut off from the long lengths of wires for subsequent chemical digestion and radionuclidic assay. As given in detail by Collé (1999), the assay of the seeds involved the dissolution of the TiNi jacket, extraction of the activity from the internal ^{32}P-containing source material, quantitative solution transfers and a gravimetrically-based dilution, followed by liquid scintillation (LS) spectrometry of the resulting master solution with ^{3}H-standard efficiency tracing using composition-matched LS cocktails. The protocol included provisions for accounting (and correcting) for all possible losses of ^{32}P in the digestion procedure (based on radiochemical tracing experiments), for any unrecovered activity in the remaining source material and for any residual activity in the solution-transfer and containing vessels.

The methodology for the LS spectrometry efficiency-tracing techniques, as currently invoked in this laboratory, has been treated at length by Collé and Zimmerman (1996) and by Zimmerman and Collé (1997a,b). Their work included the development and use of an explicit measurement-uncertainty-treatment model for the method. The method's specific application for ^{32}P assays, which

included the procedures used for the resolution of the attendant, always-present, ^{33}P-impurity, has also been described by Collé (1997a). The critical importance of LS cocktail matching to account for cocktail-composition-mismatch effects has been addressed by Collé (1997b).

The two seeds, as reported by Collé (1999) and certified by NIST, had assayed ^{32}P activities of: 1.211 ± 0.047 MBq as of 1200 EST 12 August 1997 for P-97-15-2 and 14.15 ± 0.20 MBq as of 1200 EST 6 October 1997 for P-97-23-6. The cited uncertainty intervals in the ^{32}P activity are expanded uncertainties with a coverage factor of $k = 2$, which are presumed to correspond to intervals with a level of confidence of approximately 95% (refer to Taylor and Kuyatt (1994) for internationally-accepted definitions of the measurement uncertainty terms).

The seeds had ^{33}P/^{32}P-impurity ratios, at their above-given reference times, of 0.413 ± 0.018 and 0.111 ± 0.009, respectively. The apparently and relatively large ^{33}P/^{32}P-impurity ratios are merely a result of the fact that the sources were considerably aged over many ^{32}P half-lifes ($T_{32} = 14.262 ± 0.014$ d) with less decay of the longer-lived ($T_{33} = 25.34 ± 0.12$ d) ^{33}P-impurity. Decay corrections to the preparation times of the seeds reveal that these impurity ratios are very consistent and representative of a typical ^{33}P-impurity magnitude of ≤0.008% that is found in most commercial supplies of [32]P (Collé, 1997a, 1999). At the time of the ionization current measurements, the impurity ratio in the two seeds over the three data sets varied from 1.3 to 11.5%. The CRC-12 ionization current measurements of the sealed seeds were wholly invariant of the ^{33}P-impurity since virtually none of the lower energy ($E_{\beta(max)} = 248.5 ± 1.5$ keV) [33]P β-particles escaped from the TiNi encapsulation. The foregoing conclusion was based upon both empirical observations (Collé, 1999) as well as the results of Monte Carlo calculations (Seltzer, 1997) for the emitted ^{32}P and [33]P β-spectra from the given seed geometry. The following Appendix A demonstrates the insignificance of the ^{33}P-impurity on the ionization current measurements.

3. Results and discussion

Fig. 1 displays the first trial of the ionization current measurements (in units of nA of current I per MBq of ^{32}P activity A_{NIST}) on source P-97-15-2, which was used to establish the optimal spacer length H. The values of I are the CRC-12 ionization current readings at some measurement time t_I, whereas the A_{NIST} values are the above cited assay result for the ^{32}P activity in the seed with decay corrections to the t_I times. The uncertainty bars on the individual datum points in
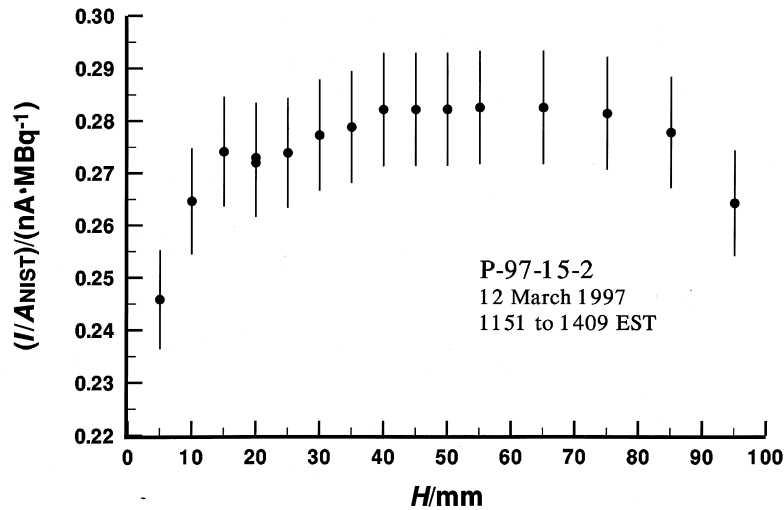
Fig. 1. Capintec CRC-12 'dose calibrator' response (in units of nA of ionization current I per MBq of ^{32}P activity A_{NIST}) for Guidant seed P-97-15-2 as a function of the spacer height H in mm. The uncertainty bar on each datum corresponds to the $k = 2$ expanded uncertainty in A_{NIST}, i.e., the estimated $\cong 95\%$ confidence interval).

Fig. 1 reflect only the uncertainty in A_{NIST}. As reflected, the ionization current response I/A_{NIST} is relatively flat across H and a value of $H = 55$ mm was somewhat arbitrarily selected as the optimum. It is optimal in the sense that I is maximized and least sensitive to any vertical source positioning errors.

The results of the three dial setting determinations obtained with a constant $H = 55$ mm spacer are shown in Fig. 2. Values of A_D are the 'apparent activity' readings obtained from the CRC-12 at a dial setting D at measurement times t_D, while the values of A_{NIST} are again the assay results for the ^{32}P activity content of the seeds after being decay corrected to the t_D measurement times — such that $A_D/A_{NIST} = 1$ corresponds to exact agreement between the CRC-12 'apparent activity' reading A_D and the decay-corrected
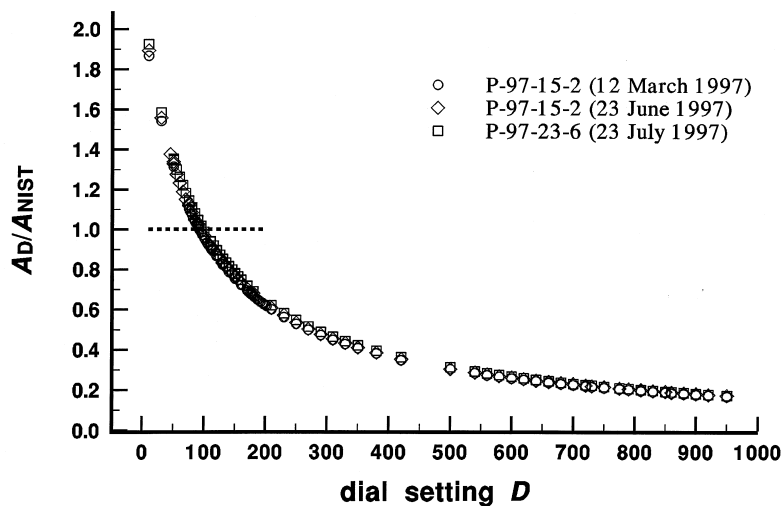

Fig. 2. Three determinations of the calibration curve for the Guidant ^{32}P seeds with the Capintec CRC-12 'dose calibrator' as a function of the instrument's 'dial setting' D. The ordinate A_D/A_{NIST} is the ratio of the instrument's 'apparent activity' A_D at setting D and the NIST-assayed ^{32}P activity A_{NIST} in the seeds at the A_D measurement times. All of the determinations were made with the seeds at a constant spacer height of $H = 55$ mm in teflon catheters which were contained within a Capintec linear brachytherapy-source holder.
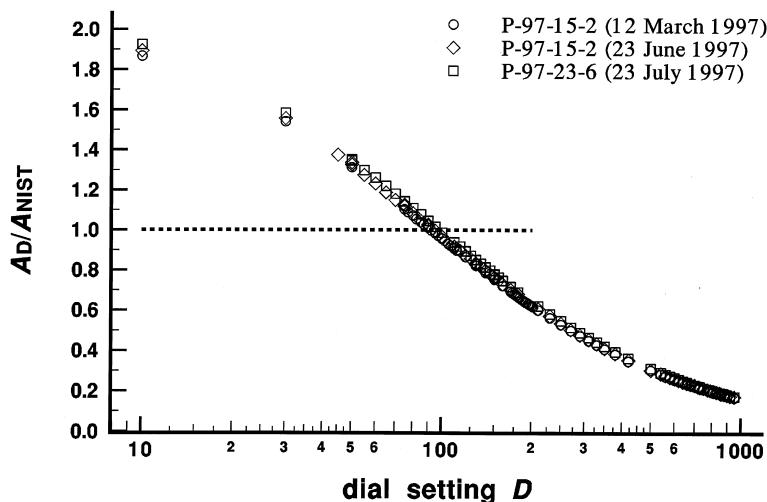
Fig. 3. The three calibration curve determinations of Fig. 2 as displayed with a logarithmic abscissa, whose linearity in the central D region illustrates the nearly exponential A_D/A_{NIST} versus D dependence.

A_{NIST} ^{32}P activity assay result. The A_D/A_{NIST} response as a function of D is nearly exponential (in the log-centric region) as reflected in Fig. 3 when D is plotted on a logarithmic abscissa. Fig. 4 shows the results of these three determinations over the nearby $A_D/A_{NIST} \cong 1$ region; i.e. for dial settings $75 \leq D \leq 125$ with $0.85 \leq A_D/A_{NIST} \leq 1.15$.

The results of these three determinations are summarized in Table 1. It is apparent from Fig. 4 and Table 1 that there exists a small systematic disagreement between the dial setting result for seed P-97-23-6 (with a determined D of about $D \cong 97$) and the two

results for seed P-97-15-2 (with a D of roughly $D \cong 88$). Because of ancillary considerations, this difference can be attributed to the stability (and/or long-term measurement precision including that due to source-positioning reproducibility) in the CRC-12 readings of A_D; and not to an inherent systematic error in the A_{NIST} determination for either seed. Relative activity measurements A_X by Guidant (using a different ionization-chamber-based instrument) in comparison to A_{NIST} values for the two seeds exhibit an agreement of about 1.5% (i.e. for the ratio of A_X/A_{NIST} for one seed to A_X/A_{NIST} of the other) (see
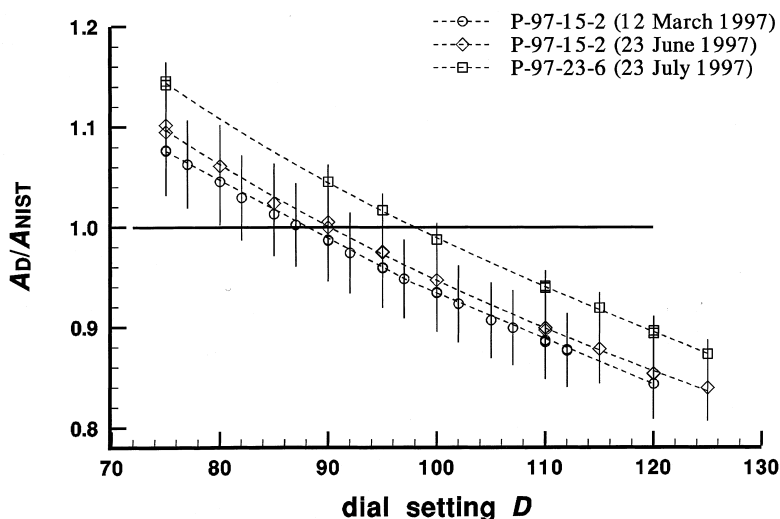

Fig. 4. An expanded view of the three calibration curve determinations of Fig. 2 (in the region $0.85 \leq A_D/A_{NIST} \leq 1.15$ for dial settings $75 \leq D \leq 125$) which demonstrates the appropriateness of a calibration factor dial setting of $D = 95$ to achieve $A_D/A_{NIST} \cong 1$. The uncertainty bars on the plotted data correspond to only that due to the A_{NIST} determinations (refer to Fig. 1).

Table 1
Summary of the three determinations of the 'dial setting' calibration factor for assay of the Guidant ^{32}P seeds with the Capintec CRC-12 'dose calibrator'

Source identification	P-97-15-2	P-97-15-2	P-97-23-60
Instrument	Capintec CRC-12 dose calibrator with the acrylic chamber-well insert (liner) supplied with the instrument removed		
Source holder	Capintec linear brachytherapy-source holder supplied by Capintec		
Measurement conditions	source inserted inside a teflon catheter tube (1.00 mm i.d. × 1.67 mm o.d.) above a 55 mm spacer in the source holder		
Dose calibrator measurement time t_D	1326 to 1349 EST, 12 March 1997	1108 to 1156 EST, 23 June 1997	0936 to 1012 EST, 23 July 1997
^{32}P activity A_{NIST} at time t_D (Bq)[a]	$(3.328 \pm 0.137)10^9$	$(2.239 \pm 0.086)10^7$	$(5.440 \pm 0.088)10^8$
Calibration factor I/A_{NIST} (nA·MBq)[b]	0.283 ± 0.012	0.287 ± 0.011	0.300 ± 0.005
Dial setting D for $A_D/A_{NIST} = 1$[c]	87.3 ± 7.5	90.1 ± 6.9	97.4 ± 2.4
Apparent error in A_D at $D = 95$ (%)	-4.1	-2.7	$+1.7$

[a]From the ^{32}P activity values given in Collé (1998) with decay corrections to t_D using a half-life of 14.262 ± 0.014 d. The cited uncertainty intervals are for a $k = 2$ coverage factor and include the additional uncertainty component for the ^{32}P decay correction to time t_D.[b]Based on measurements of the ionization current I per unit activity with source P-97-15-2 on 12 March 1997 (1151 to 1409 EST) with normalizations to the measurements of the apparent activities A_D across all dial settings ($10 \leq D \leq 950$).[c]At a given dial setting D, the apparent activity A_D was obtained from direct readings of the dose calibrator's display (in units of either mCi or μCi) *multiplied by a factor of 10*. The cited expanded uncertainty intervals on A_D/A_{NIST} are for a coverage factor of $k = 2$ and reflect only the uncertainties in the A_{NIST} determinations.

(Collé, 1999)), while the ratios of the two A_D/A_{NIST} values for any given dial setting differ by over 5%.

In retrospect, we recognized that one would be well served by using a long-lived reference source (e.g. ^{226}Ra) to perform between-seed and between-measurement normalizations for such calibration measurements. Such normalizations would have undoubtedly removed any question as to the cause of the discrepancy between seeds, but nevertheless might not have entirely removed the inherent imprecision in the dose calibrator readings (such as that due to source-positioning errors). Such radium-reference-source normalizations are oft used for ionization chamber measurements at standardization laboratories like NIST (NCRP, 1985), but are rarely used for routine dose calibrator-type measurements.

The three dial setting determinations given in Table 1 could not be treated with equal weight in deriving an appropriate 'average' dial setting, since the two determinations of A_D/A_{NIST} with source P-97-15-2 were based on only one A_{NIST} assay and since the relative expanded uncertainties in A_{NIST} for the two seeds differed by nearly a factor of 3. The underlying uncertainty components in the uncertainties in the A_{NIST} values for the two seeds were also highly correlated (Collé, 1998). Using a variety of weighted-combination models, which are all equally valid but devolve from different input assumptions, it was clear that the 'best' dial setting D dwelt within the range $93.1 \leq D \leq 96.8$. We opted to choose a mid-range, near-median value of $D = 95$.

The last row of Table 1 shows the apparent error in A_D at the chosen $D = 95$ for the three determinations. Table 2 gives our well-considered uncertainty assessment for any typical measurements of the Guidant seeds with the Capintec CRC-12 dose-calibrator at a $D = 95$ dial setting under the given source-geometry conditions.

Table 2
Uncertainty assessment for the ^{32}P activity in a Guidant seed as obtained by typical measurements with the Capintec CRC-12 dose calibrator with a D = 95 dial setting[a]

Uncertainty component	Relative uncertainty (%)
u_1 is the standard uncertainty in A_{NIST} to determine D	0.8 to 2.1
u_2 is the standard uncertainty in regression for A_D/A_{NIST} as a function of D	0.3
u_w is the standard uncertainty in D for within-source variability	2.9
u_b is the standard uncertainty in D for between-source variability	8.9
standard uncertainty in D $u_D = (u_w^2/2 + u_b^2 + u_2^2 + u_1^2)^{1/2}$	9.3
corresponding standard uncertainty in A_D at $D = 95$	2.6
expanded uncertainty ($k = 2$) in A_D	5.2

[a]For the measurement and source-holder conditions given in Table 1.

4. Summary

A 'dial setting' calibration factor for the Guidant ^{32}P brachytherapy sources with the Capintec CRC-12 'dose calibrator' has been determined. This determination now allows for the nondestructive assay of these seeds to a $k = 2$ expanded uncertainty interval of about $\pm 5\%$ (with $\cong 95\%$ confidence) provided that the necessary measurement conditions are satisfied — primarily for the provisionals that one use the Capintec linear brachytherapy-source holder with the seed contained in a similar teflon catheter above an $H = 55$ mm spacer at a dial setting of $D = 95$.

The techniques employed and described here may also be of interest to other researchers for the determination of similar-type calibration factors for other instruments and for other kinds of sealed radionuclidic sources.

Acknowledgements

Appendix A. Assessment of a possible ^{33}P-impurity effect on the ionization current measurements

The possible effect of the ^{33}P-impurity in the Guidant seeds on the calibration results, in addition to any ^{33}P-impurity effect on subsequent measurements of similar seeds with the Capintec CRC-12, was of concern. It is true that virtually none of the ^{33}P β-particles escape from the source's TiNi encapsulation. Nevertheless, the ^{33}P decay within the source undoubtedly results in the emission of internally-generated, low-energy photons (X-rays resulting from ionization, bremsstrahlung from the stopping of the β-particles, as well as photonic emissions following secondary electron production and subsequent interactions) which might be expected to generate some small ionization current response in the CRC-12. The ionization chamber response for ^{32}P after all results from the same kind of electronic interactions, but these mainly

occur externally to the source; i.e. within the source holder and inside the instrument's re-entrant well. Inasmuch as the three calibration factor determinations were made with seeds with fairly wide-ranging ^{33}P-to-^{32}P activity ratios, it is possible to use the available data to demonstrate the insignificance of the ^{33}P-impurity on the ionization current measurements.

The ionization current I may be considered to consist of the sum of two components: the current resulting from the ^{32}P activity A_{32} and that due to ^{33}P, A_{33}, such that

$$I = K_{32}A_{32} + K_{33}A_{33}, \tag{A.1}$$

where K_{32} and K_{33} are proportionality constants that relate the instrument's current response to each radionuclide. Eq. (A.1) may be immediately rewritten as

$$I/A_{32} = K_{32} + K_{33}(A_{33}/A_{32}), \tag{A.2}$$

where the left-hand side of Eq. (A.2), I/A_{32}, corresponds to the ionization-current calibration factors given in Table 1, and where A_{33}/A_{32} is the impurity ratio in the seed at the time of the ionization current measurements (as obtained by decay corrections of the radionuclidic assay results of Collé (1998)). The values of A_{33}/A_{32} for the three determinations were in the range $0.013 \leq A_{33}/A_{32} \leq 0.115$. In the absence of any ^{33}P-impurity effect, I/A_{32} is just equal to K_{32}. With a ^{33}P-impurity effect, the right-hand side of Eq. (A.2) has an additional term that is equal to the product of K_{33} and the A_{33}/A_{32} impurity ratio. Eq. (A.2), as a plot of I/A_{32} versus A_{33}/A_{32}, is linear with an intercept (at $A_{33}/A_{32} = 0$ for no ^{33}P-impurity) equal to K_{32} (as expected), and with a positive slope $d(I/A_{32})/d(A_{33}/A_{32}) = dI/dA_{33}$ equal to K_{33}.

Fig. 5, using the calibration data of Table 1, shows the result of this determination for K_{32} and K_{33}. As shown, I/A_{32} and A_{33}/A_{32} are uncorrelated (with a correlation coefficient of about -0.2), and K_{33} is indeterminate with a negative slope of -0.03 ± 0.15 nA·MBq compared to $K_{32} = 0.292 \pm 0.011$ nA·MBq. Hence, the effect of the ^{33}P-impurity on the ionization current measurements is negligible and can be ignored. The upper limit on K_{33} from the regression is $K_{33} \leq 0.12$. For a seed with an initial ($t = 0$) impurity ratio of $A_{33}/A_{32} = 0.008$, even after the passage of 120 days (in which the impurity ratio increases to 0.10), the possible contribution of ^{33}P to the ionization current (as an upper limit) will be less than 4%, which is well within the uncertainty for such ionization current measurements with commercial 'dose calibrator' instruments.

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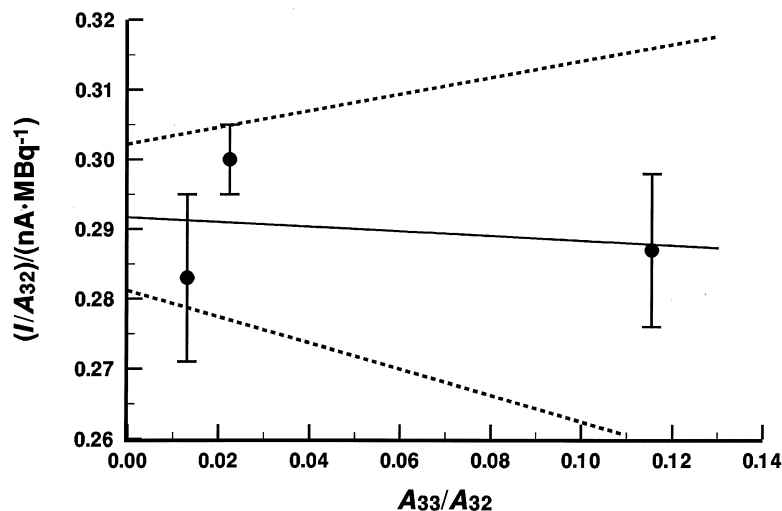CIRMS, Council on Ionizing Radiation Measurements, 1998. Report on National Needs in Ionizing Radiation

Fig. 5. Invariance of the Capintec CRC-12 ionization-current response with the ^{33}P-impurity in the Guidant seeds, as exhibited by the ionization current I (in units of nA) per MBq of ^{32}P activity A_{32} as a function of the impurity ratio A_{33}/A_{32}. The uncertainty-bar interval on each I/A_{32} datum is that given in Table 1. The solid line is the linear regression result for fitting the three data to the functional form $I/A_{32} = K_{32} + K_{33}(A_{33}/A_{32})$. The upper and lower broken lines correspond to the uncertainty limits on the regression for the K_{32} and K_{33} fitted parameters.

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