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Uncertainties in alanine dosimetry in the therapeutic dose range

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Abstract

A method for evaluating the overall uncertainty of alanine EPR transfer dosimetry in the therapeutic dose range is described. The method uses experimental data on EPR signal reproducibility from replicate dosimeters irradiated to low doses (1–5 Gy), estimates of Type B uncertainties, and Monte Carlo simulations of heteroscedastic orthogonal linear regression. A Bruker ECS106 spectrometer and Bruker alanine dosimeters have been used for this evaluation. The results demonstrate that alanine dosimetry can be used for transfer dosimetry in that range with the overall uncertainty 1.5–4% (1σ) depending on the dose, the number of replicate dosimeters, and the duration of the calibration session (the session should not exceed one working day). Published by Elsevier Science Ltd.

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1. Introduction

Electron paramagnetic resonance (EPR) spectrometry with alanine is now widely recognized as the most accurate method of transfer dosimetry in the industrial (kGy) dose range. It is well established for calibrating industrial radiation sources against national standards and for comparisons between national laboratories. The accuracy of the method is generally very high, largely due to the low sensitivity of the alanine response to irradiation variables (energy, dose rate, temperature, etc.), and the ability of EPR spectrometers to measure dosimeter signals very precisely.

However, the application of alanine dosimetry to the calibration of medical therapy sources is not straightforward, because typical medical doses are at the low end of the working range for this method. Doses above 20 Gy can be measured with alanine with a speed and accuracy comparable to those in dose measurements in the kilogray range. However, for many low-intensity medical sources, it would take an unreasonably long time to produce such a high dose. On the other hand, measuring EPR signals for subgray doses is extremely laborious and time-consuming. According to Haskell et al. (1998) and Hayes et al. (2000), measuring doses around 100 mGy with reasonably high accuracy requires a multi-step procedure that takes several days and is not competitive with the commonly used thermoluminescence dosimeters. However, the range between these two extremities may offer a reasonable compromise between the demands of accuracy and cost efficiency.

A clear specification of the measurement session duration with a well-defined overall uncertainty would facilitate the use of alanine dosimetry in the 1–5 Gy dose range. These issues have not been resolved despite the relatively large number of publications on alanine dosimetry in the radiotherapy dose range (Ahlers and Schneider, 1991; Bartolotta et al., 1993, 1999; Ciesielski and Wielopolski, 1995; Ciesielski et al., 1993; Cuttone et al., 1999; De Angelis et al., 2000; Fainstein et al.,

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2000; Feist et al., 1993; Gall et al., 1996; Gao and Zaiyong, 1996; Haskell et al., 1998; Hayes et al., 2000; Mehta and Girzikowsky, 1996; Nette et al., 1993; Olsen et al., 1990; Onori et al., 1996, 1997; Rakvin, 1996; Ruckerbauer et al., 1996; Sharpe et al., 1996; Wieser et al., 1993). These publications fall into two categories. Publications of the first category do derive uncertainties in a statistically solid manner, but, unfortunately, only for selected steps of the procedure (most commonly, for signal amplitude measurements) and ignore other sources of errors. However, even if all the sources of uncertainty had been quantified, the total uncertainty in the dose remains nontrivial, because of its strong dependence on the calibration design (number of calibration doses, number of replicate measurements, etc.).

Those in the second category exercise the "blind test" approach, reporting a few determined doses in comparison with the exact doses given to the tested dosimeters. This also does not provide much information about the uncertainty of the technique in general, since this is nothing more than a small statistical sample of random numbers. Due to the basic property of the Gaussian and similar distributions, results with small deviations from the true value are far more likely than results with larger ones. Therefore, whenever a small number of replicate measurements are taken, the variance and the uncertainty characteristics derived from it are almost certainly underestimated. In order to overcome this unfavorable condition, mathematical statistics prescribe a much larger number of replicates (Natrella, 1963) than are typically used in blind comparisons.

Our efforts to resolve these deficiencies in the literature originated from a calibration of a low-intensity radiation source at the Scientific Center of Radiation Medicine (SCRM) in Kiev. The dose rate of the source was determined using the NIST official dose certification service (Humphreys et al., 1998), which involves mailing NIST dosimeters to Kiev, irradiating them with the SCRM's source, and performing the EPR measurements at NIST. As the doses given to these dosimeters were in the (30–50) Gy range and the standard NIST procedure was strictly observed, the accuracy of the dose measurements was high (total uncertainty 1.7%, 2σ). However, the results of these measurements were not immediately disclosed to the SCRM; instead, they were provided with (0.500, 1.00, 2.00 and 5.00) Gy NIST-irradiated dosimeters. Using these reference dosimeters (along with unirradiated ones), the SCRM participants performed their own calibration of the source in the (0.5–5) Gy dose range. In this calibration, they used a technique that requires only one working day for the whole calibration session and, thus, is practical. The signal scatter for replicate dosimeters in those measurements (52 dosimeters in total in four groups) was used in Monte Carlo simulations for deriving the uncertainty of dose determinations that can be achieved in general (under similar replicate scatter conditions). Thus, unlike in the previous publications in EPR dosimetry, we characterize the uncertainty of a dosimetric technique not only by determining a limited number of unknown doses (which are random). Here, the reproducibility of signal measurements from a reasonably large data set is also combined with additional uncertainty estimates to simulate the calibration with a random number generator and derive the uncertainty in the doses (under these or similar conditions).

2. Experimental[1]

2.1. Official NIST dose certification

Three sealed polystyrene vials, each containing four unirradiated alanine pellets (GammaService, Dresden, Germany; diameter 4.9 mm, height 3.0 mm; 96% alanine), were mailed for irradiation in the SCRM Cs-137 source to be calibrated (UDP-Inter, Serial No. 25; dose rate $\sim$180 mGy/h). The dosimeters were given nominal doses 30.34, 47.03, and 55.47 Gy at the controlled irradiation temperatures of 13°C, 14°C, and 15°C, respectively. The irradiated vials were returned to NIST, and the doses were measured using the standard NIST procedure (Humphreys et al., 1998). The EPR signals were measured on a Bruker ECS106 spectrometer with a TMH4103 resonator at two orientations of each pellet differing by about 90°. The quartz pellet holder provided a highly reproducible positioning of the pellets in the cavity. The holder remained in the cavity during the whole measurement session, and the pellets were manipulated pneumatically. The signal of an adjacent reference sample, a synthetic ruby crystal mounted to the front wall of the resonator (Nagy et al., 2000b), was recorded after registration of each alanine signal with the pellet still residing in the cavity. Both signals were recorded at a 0.25 mW microwave power, 1.4 mT modulation amplitude, 1.3 s time constant, 20.48 ms conversion time, 1024 point resolution, and a single scan for each pellet orientation. The scan widths for alanine and ruby were 2 and 7 mT, respectively, and the sweep time was 21 s for each scan. The calibration curve was constructed on the basis of the signals of 20 pellets irradiated to 5 doses in the 20–100 Gy range at a fixed temperature

[1] The mention of commercial products throughout this paper does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that products identified are necessarily the best available for this purpose.

(4 replicate pellets at each dose) at the dose rate of 13 Gy/h with the B036 ^{60}Co radiation source (US national standard calibrated with a water calorimeter.) The average relative standard deviation (RSD) of the signals of replicate pellets of the same vial was 0.38% (both for the calibration and test pellets). The signals for all pellets were normalized to the same irradiation temperature.

2.2. Lower-dose source calibration at SCRM

Commercial Bruker alanine dosimeters ($D = 4.9$ mm, $h = 5$ mm; 80% alanine, 20% polyethylene as a binder) were used for the lower dose calibrations, as the larger amount of alanine (relative to other commercial dosimeters) boosts the sensitivity of the technique. Four groups of the pellets irradiated to 0.500, 1.00, 2.00, and 5.00 Gy at NIST were used as reference dosimeters. Four groups of test pellets of the same type (9 replicates in each) were irradiated to the nominal doses of 0.5, 1, 2, and 5 Gy with the UDP-Inter source at SCRM at controlled temperatures. NIST and the SCRM used irradiation vials of the same type.

The EPR measurements were performed at SCRM with a Bruker ECS106 spectrometer (an ST4102 resonator) according to the following procedure. All measurements were conducted with the same convex-bottom sample tube (5 mm I. D.), which was removed from the cavity for pellet replacements. The position of the tube in the cavity was set with the standard Bruker concave Teflon support, which was immobile during the measurement session. The sample tube had a Mn(2+)/MgO reference sample attached to it, whose signal (the second lower-field line) was used for frequency normalization of the spectra of the irradiated and unirradiated alanine pellets, as well as of the empty sample tube. All manipulations involving more than one spectrum were performed after normalizing all the spectra to the same frequency. All the spectra were recorded at a 10 mW microwave power, 0.7 mT modulation amplitude, 0.328 s time constant, 10.24 ms conversion time, 1024 point resolution, and seven scans. The scan widths were 1 and 0.5 mT for the central alanine line and the second Mn(2+) line, respectively; the sweep times were 11 and 6 s, respectively. The EPR signal of each pellet was recorded at three pellet orientations differing by approximately 120°, preceded and followed by recording the signal of the empty sample tube and of the spectrum of an alanine pellet irradiated to 20 Gy, which served to monitor uncontrolled variations in the spectrometer sensitivity (only five scans were used for this strong signal). In the beginning of the calibration session, spectra from a set of ten unirradiated dosimeters were recorded under the same conditions (seven scans at each of three orientations); these spectra, combined and normalized to a single pellet, formed the "average spectrum of an unirradiated pellet" which was subtracted from each spectrum of an irradiated dosimeter. The details of the subtraction technique have been described earlier (Chumak et al., 1999). After the average signal of an unirradiated pellet and the signal of the sample tube were subtracted from the original spectrum of a dosimeter, the difference was least-squares-fitted with a line profile obtained from a spectrum of a pellet irradiated to 20 Gy (only the signal intensity was varied), and the amplitude of the fit was used as a measure of the signal. Fig. 1 gives an example of the spectrum processing. Signal recording and processing for a single dosimeter took about 12 min, the duration of a whole calibration session involving measurements of 16 calibration and 27 test dosimeters (four calibration doses and three test doses) was about 9 h.

2.3. Monte Carlo simulations

Uncertainty analysis and Monte Carlo simulations of the calibration experiment were performed at NIST using a C++ program (Nagy and Desrosiers, 2001) that utilizes Williamson's algorithm for processing linear regressions with errors in both variables (Williamson, 1968). This algorithm was found to be the best among the competitors in a broad critical evaluation (Riu and Rius, 1995). In contrast to the regression simulation program reported in the EPR dosimetric literature earlier (Chumak et al., 1996), this one is free of the somewhat unrealistic restrictions on the types of the distributions for either of the two variables, and is also self-consistent in terms of the type of the generated calibration points and the procedure of their subsequent least-squares processing. Basically, the procedure involves generating random calibration points using a theoretical response line and specified variances in both X and Y for each calibration dose. The technique of imposing the errors in the theoretical X and Y values follows Berkson Case 2 (often referred to in the literature as just "Berkson Case"), which corresponds to the "creation" of X values with errors (in contrast to "measuring" them with errors) (Berkson, 1950). The generated set of random calibration points is then processed with the Williamson's least-squares procedure to produce a random slope and intercept of the calibration line. With this prepared, a set of random "measured signal" replicates for a "test vial" was generated on the basis of the specified theoretical Y value and its variance. The calculated mean of these signal replicates was used in combination with the calculated (random) regression parameters to produce a random X value ("determined dose"). This procedure was repeated 100,000 times, and a statistical processing of the 100,000 random X values produced uncertainty in the determined X. Normal distribution of all the random

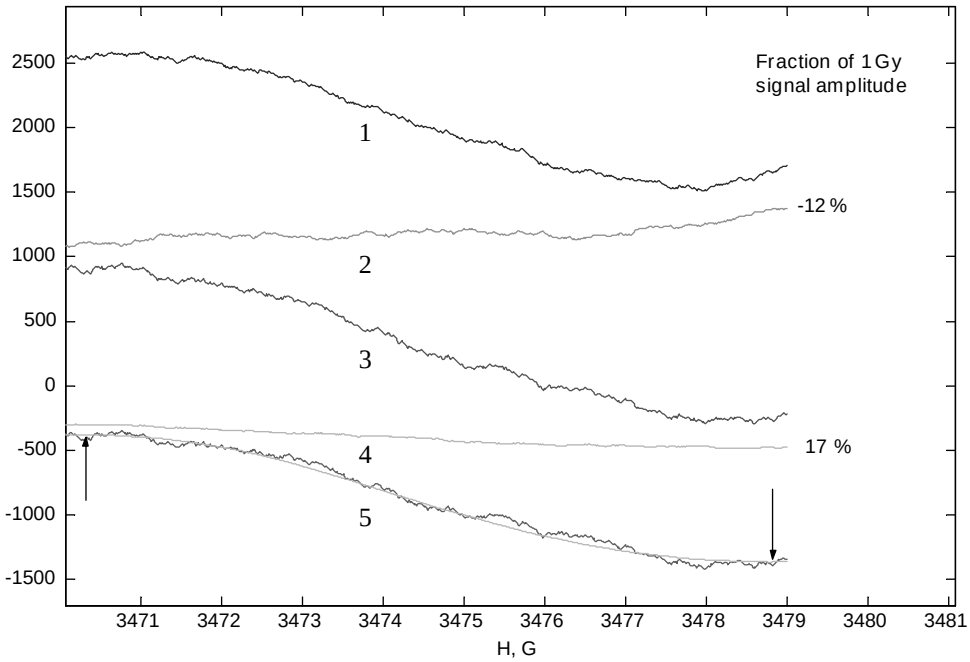

Fig. 1. An example of processing a 1 Gy alanine signal. 1—original (total) spectrum of the irradiated dosimeter in a single orientation; 2—spectrum of the empty sample tube; 3—"pure" signal of the irradiated dosimeter (Spectrum 1−Spectrum 2); 4—the average spectrum of an irradiated dosimeter (without the signal of the empty sample tube); 5—"pure" radiation-induced signal (Spectrum 1−Spectrum 2−Spectrum 4) and the best fit. All the spectra are normalized to the same number of accumulations and the same microwave frequency. The arrows show the positions of the extrema of the central alanine line for that frequency.

values was assumed. Normal distribution of the EPR signal replicates, which was known to occur in the high-dose range, has recently been confirmed also for the doses in the therapeutical range (Fainstein et al., 2000). Although X values determined from Y values using a calibration plot, as ratios of random numbers, are not normally distributed (Fieller, 1940; Creasy, 1954; Marsaglia, 1965), the degree of the skewedness of their distribution under conditions of this simulation never exceeded a fraction of a percent; so, the simulation results are presented in terms of standard deviations rather than slightly asymmetric confidence intervals, which are more difficult to compare. A random number generator with a period of 2.1×10^9 was used (Press et al., 1992). The function calculating the regression parameters was tested against the Pearson and York's "standard" data set (Pearson, 1901; York, 1966; Riu and Rius, 1995). Sets of the random calibration plots simulated with this program did not show any bias in the regression parameters, as expected for Berkson Case 2 in contrast to Berkson Case 1. The program as a whole was also successfully tested against a number of normal and extreme calibration cases, for which exact analytical expressions are available.

3. Results and discussion

3.1. Modified dosimetric procedure

The main focus of this work was to characterize the overall uncertainty of alanine transfer dosimetry in the moderately low-dose range (0.5–5 Gy) in a statistically meaningful way. As mentioned above, the uncertainty strongly depends on the time available for the calibration session. We intentionally restricted that time to one working day (the period that seemed reasonable for a dosimetry technique to be competitive with TLD) and tried to maximize the accuracy under this self-imposed limitation. The standard procedure used at NIST for high doses was modified using common methods for increasing the signal-to-noise ratio (increasing time constant, number of accumulations, etc.), but only to the extent where the whole calibration session does not exceed a working day. As a result of this strategy, this procedure differs significantly from the one described by Hayes et al. (2000), who sought to achieve the lowest detection limit and the highest reproducibility possible without regard for the measurement duration (a calibration session, performed according to their technique, would be expected to take several days).

Here, alanine dosimeters with similar EPR signals were not pre-selected before irradiation (unlike that of Hayes et al.). Individual selection of a fairly large number of such dosimeters necessary for a calibration session is a laborious and time-consuming task. All the dosimeters used in this work were randomly selected from Bruker Alanine Dosimeter Batch 4.

Second, the spectral accumulation time was decreased, to some extent, while considering the effect of this change on the signal-to-noise ratio (and, hence, the signal reproducibility). By decreasing the number of accumulations from 15 to 7, an approximately 2-fold gain in the measurement time was achieved, whereas the signal-to-noise ratio deteriorated only by a factor of 1.4.

Third, the scheme for sweeping the spectrum was optimized. Hayes et al. used a 10 mT wide scan that included the three most intense peaks in the alanine spectrum along with the peaks of the reference sample (also Mn(2+) in MgO); this requires a large magnetic field scan width. We scanned only the central peak in the narrowest range necessary and could accumulate twice more measurements per unit time. The reference sample line (necessary for frequency normalization) was recorded separately, also over a very narrow range.

Fourth, the dosimeters used in this study were 4.9 mm long, in contrast to the 10-mm-long dosimeters used by Hayes et al. The rationale for this choice was that, although smaller dosimeters result in somewhat lower sensitivity, they are more efficient in measuring radiation field inhomogeneities.

Fifth, the calibration technique involving irradiation of the same dosimeter in a stepwise manner was not used. This technique significantly increases the time of a calibration session (for high precision alanine dosimeter measurements it is recommended to wait at least 2 h after irradiation because of the sharp decrease in the signal amplitude (Nagy and Desrosiers, 1996). Also this approach artificially reduces the apparent uncertainty. Clearly, if the signals of the same pellet are repeatedly measured with each new dose, the scatter of points with respect to the calibration line will be smaller than it would be with different dosimeters used for each dose. However, the irradiated test dosimeters do not have exactly the same background signal, size, shape, alanine/binder ratio, etc., that is, the characteristics that produce the well-known "interspecimen scatter". This results in a systematic error for the dose determined with each test dosimeter that is not accounted for in the uncertainty estimate. Considering this, the classical approach of irradiation with several replicate dosimeters for each of the calibration doses was adhered to.

Sixth, despite the known inaccuracies resulting from the signal anisotropy, the rotating goniometer technique advocated by Hayes et al. was not used because of its inherent theoretical inconsistency. Normalization to frequency using the position of a reference sample line is based on the assumption that microwave frequency does not change during the recording of the spectrum. This certainly is not the case when an object is being rotated in the cavity during spectrum registration. Instead, accumulations were made at three discreet orientations of the immobile sample and the spectra were summed *after normalizing each to frequency*. Since during each accumulation with a static sample the microwave frequency was constant, there were no shifts of the alanine and manganese lines with respect to each other in the course of recording, and using the manganese lines for horizontally aligning several spectra before manipulations was technically valid.

In summary, a low-dose alanine technique was developed that uses time more efficiently, avoids some methodical pitfalls, and is simplified to the extent minimally necessary to make the calibration procedure short enough to be practical.

3.2. Alanine signal measurements in the (0.5–5) Gy range

It is well known that the poor reproducibility of alanine signals at low doses is due to a combination of several factors: instrument noise, variation in the empty cavity/sample tube signals, interspecimen variations in the "background" (radiation-irrelevant) signal, and signal anisotropy. Contributions to the uncertainty from these sources are often comparable in magnitude and difficult to separate.

Instrument noise can be decreased by the proper selection of recording parameters, but this improvement is usually costly. An increase in time constant, which results in the filtering out more of high-frequency noise, requires slower spectrum recording. The accumulation of a large number of spectra also results in longer measurement time, and the signal-to-noise ratio improvement does not balance well against the gain in measurement time. Obviously, there is a practical limit in such improvement. As the noise is not absolutely "white" (random), making more accumulations with a lower time constant usually produces better signal-to-noise ratio per unit time than a smaller number of slower accumulations at a higher time constant.

Variations in the signal of an empty sample tube is another source of inaccuracies. Some techniques call for the subtraction of the empty holder spectrum from the spectrum of an irradiated dosimeter. The importance of the empty tube spectrum is not so much this signal itself (although an extremely strong signal is undesirable), but its variations in time. Although there are conceivable reasons for such variations (e.g., time-dependent external holder contamination, variations in the microwave field distributions due to temperature effects causing changes in the signal from the cavity walls), in many cases it is difficult to separate them from the low-frequency instrumental noise and, thus, prove their

existence per se. Here, the contribution of the empty tube signal to the amplitude of the alanine signal was negative, and was approximately equal to the signal of a 90 mGy dose in its absolute value on average, with extremes of 50 and 160 mGy during a working day (Fig. 2). As can be seen from the Figure, it is hardly possible to isolate patterns that could be, with high a probability, attributed to a systematic change in the signal shape rather than to the low-frequency noise.

Alanine dosimeters exhibit a measurable EPR absorption in the alanine signal range even before irradiation (Wieser et al., 1993). This has been attributed to endogenous paramagnetic centers and/or preparation-induced centers. The intensity of that signal depends on the dosimeter brand, but, again, for dosimetry, of significance are its variations from one dosimeter to another. Also, signals of alanine dosimeters, unirradiated and irradiated, vary with the dosimeter orientation in the cavity. This can be attributed to incomplete averaging of highly anisotropic signals of alanine due to particle size and to inhomogeneity of the alanine/binder mixture. Fig. 3 shows spectra of an unirradiated dosimeter at three different orientations, while Fig. 4 demonstrates spectra of 16 randomly selected dosimeters averaged over three orientations. Although it is clear that the EPR absorption from an unirradiated dosimeter exists, the differences in the spectra of Figs. 3 and 4 cannot be unambiguously attributed to systematic changes in the absorption shape or to superimposed low-frequency irradiation noise.

Thus, the separation of the contributions from the different sources to the total scatter of signal values is neither simple, nor particularly productive for the purpose of this work. The uncertainty of the transfer dosimetry actually depends on the total scatter of signals from replicate dosimeters, regardless of the sources of this scatter and their relative contributions. The characteristics of this total scatter are shown in the rightmost columns of Tables 1 and 2, which provide the detailed data of the low-dose calibration at SCRM.

As expected, upon entering the subgray range, the scatter of the signals of replicate dosimeters significantly increases. It is noteworthy that the scatter of signals for various orientations of one pellet is not much different from the scatter of signals of different dosimeters each recorded at one random orientation. This suggests that the interspecimen scatter of the nonradiation signals is not very large as compared with the other sources of scatter (instrument noise, variations in the empty tube signal, and signal anisotropy). This lends support to the used approach of subtracting the "standard" nonradiation signal obtained by averaging noise spectra of nine unirradiated dosimeters. These data indicate that the main source of the scatter is low-frequency instrument noise.

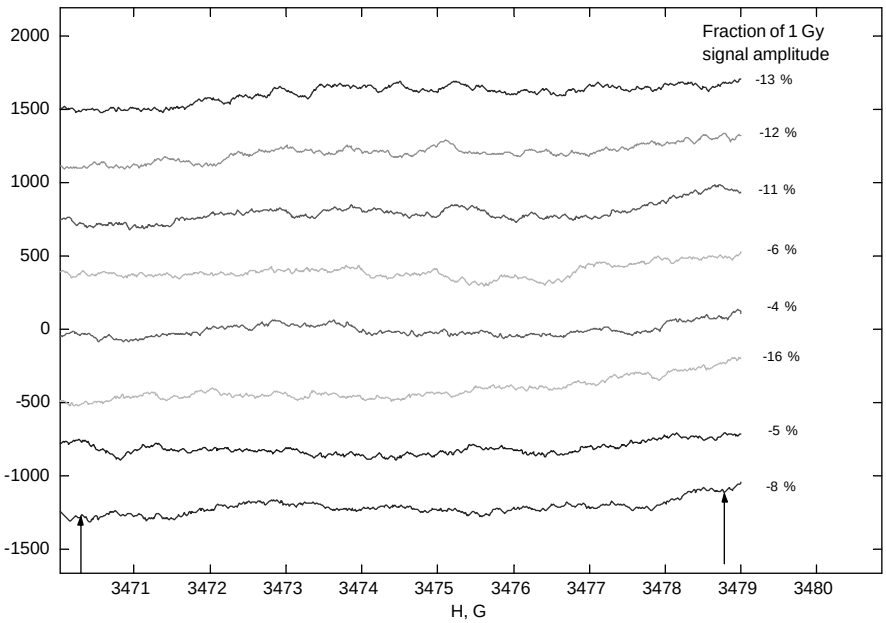

Fig. 2. Variations in the spectrum of an empty sample tube during a working day. The spectra are ordered in the chronological order, the intervals between two adjacent spectra ranged between 10 and 40 min. All the spectra are normalized to the same microwave frequency. The arrows show positions of the central alanine line extrema for that frequency; these positions were used to measure the empty tube signal contribution to the total signal (numbers to the right of the curves).

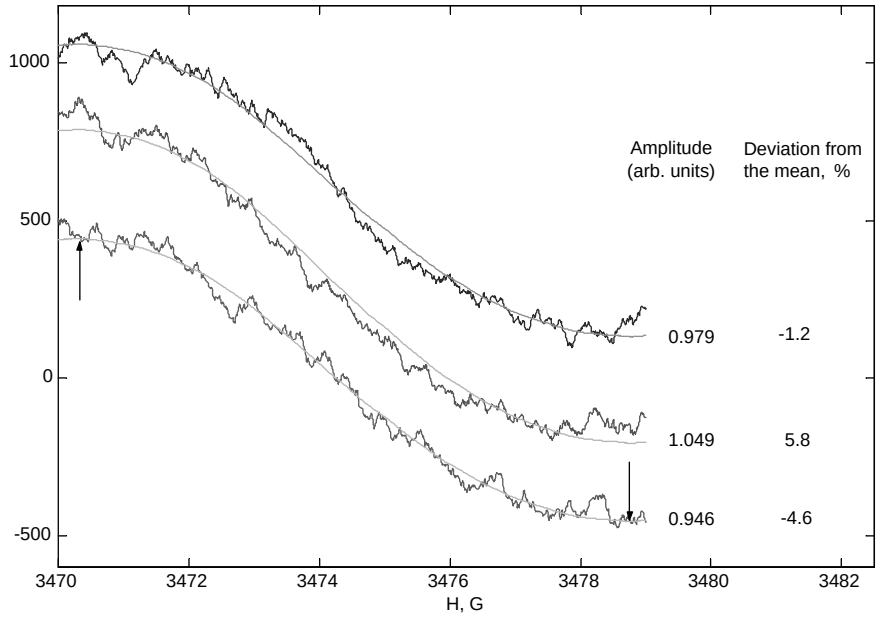

Fig. 3. EPR spectrum of an unirradiated dosimeter at three pellet orientations differing by $\sim 120^{\circ}$ with respect to the external magnetic field. The spectrum of the empty sample tube is subtracted. The arrows show the positions of the alanine line extrema at the microwave frequency used for common normalization.

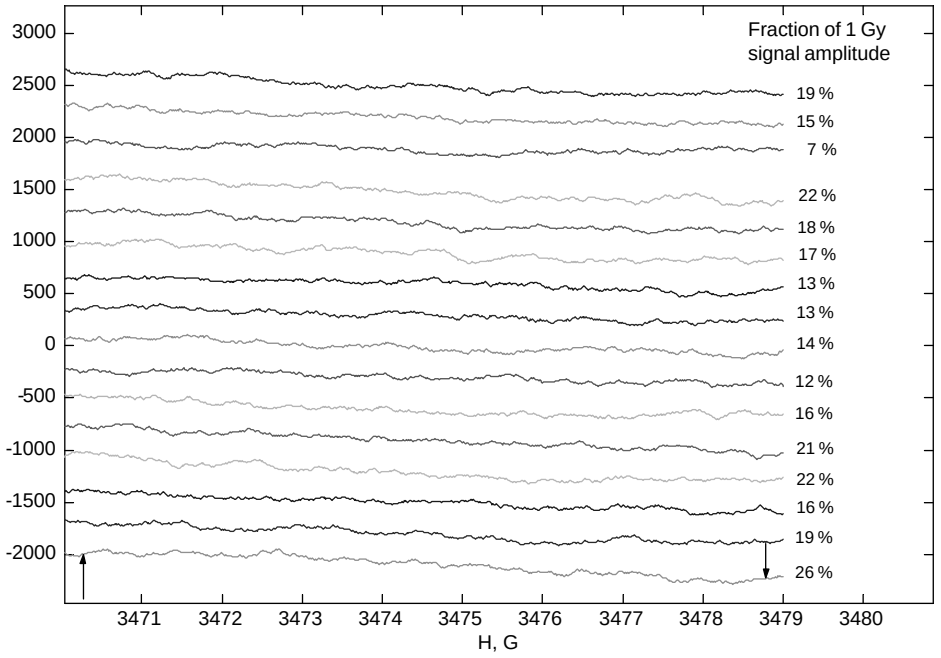

Fig. 4. EPR spectra of unirradiated alanine dosimeters. Each spectrum is the average of three spectra obtained at orientations differing by $\sim 120^{\circ}$. The arrows show the positions of the alanine line extrema at the microwave frequency used for the common normalization.

The nonlinearity of the dose response reported by Bartolotta et al. (1999) was not observed in the low-dose (0.5–5) Gy range used in SCRM, or in the higher-dose range (20–100) Gy used at NIST. In both cases the response lines appear perfectly linear, and a strict linearity test based on the comparison of the variances

Table 1
EPR signals of calibration dosimeters irradiated at NIST and measured at SCRM

Calib. dose (Gy)	Replicate dosimeter #	Radiation signal amplitudes						
		Orient 1	Orient 2	Orient 3	Mean orient 1–3	RSD orient 1–3 (%)	Mean repl 1–4	RSD repl 1–4
0.5	1	0.543	0.462	0.482	0.496	8.4	0.481	12.1%
	2	0.388	0.364	0.447	0.400	10.7		
	3	0.430	0.524	0.510	0.488	10.4		
	4	0.470	0.534	0.612	0.539	13.2		
	Mean:	0.458	0.471	0.513				
	RSD (%):	14.3	16.6	13.8				
1	1	0.958	0.940	0.865	0.921	5.4	0.982	7.1%
	2	0.999	0.956	0.991	0.982	2.3		
	3	0.992	0.971	0.871	0.945	6.8		
	4	1.000	1.101	1.135	1.079	6.5		
	Mean:	0.987	0.992	0.965				
	RSD (%):	2.0	7.5	13.2				
2	1	1.933	1.919	1.885	1.912	1.3	1.966	3.8%
	2	1.902	1.949	1.840	1.897	2.9		
	3	1.982	2.049	2.127	2.052	3.5		
	4	2.051	1.979	1.978	2.003	2.1		
	Mean:	1.967	1.974	1.958				
	RSD (%):	3.3	2.8	6.5				
5	1	4.965	5.028	4.919	4.971	1.1	5.022	1.9%
	2	5.131	5.080	5.058	5.090	0.7		
	3	4.993	4.921	4.837	4.917	1.6		
	4	5.078	5.143	5.107	5.109	0.6		
	Mean:	5.042	5.043	4.980				
	RSD (%):	1.5	1.9	2.5				

(described in many places, including Nagy, 2000) produced positive results by a large margin.

3.3. Evaluation of the total uncertainty of alanine transfer dosimetry in the 1–5 Gy range

Tables 1 and 2 combined contain a substantial body of data to characterize the general scatter of the signals of replicate dosimeters at different doses. This is necessary to derive the total uncertainty in the doses determined in this range by Monte Carlo simulations as described in the Experimental section.

To simulate calibration experiments, the uncertainties in X and Y for each calibration point and uncertainty in Y for each "measured" signal of the test pellets must be specified. Most of the uncertainties in Y are reflected in the scatter of the signals of replicate dosimeters irradiated to the same dose and, thus, can be characterized statistically (Type A uncertainties (Taylor and Kuyatt, 1994)). Errors due to the interspecimen variations in dosimeter composition and shape, weighing, and imperfect reproducibility of EPR signal registration will all manifest themselves in the RSD values of replicate pellets irradiated to the same dose. The combined RSD values for various doses are shown in Fig. 5. The confidence intervals are expectedly wide (their halfwidths are about 40% of the values at $P = 0.95$ (Natrella, 1963), as it requires significantly more replicate measurements to characterize a variance with high precision because of the peculiarities of the Gaussian distribution mentioned above. Still, this degree of uncertainty is acceptable as a starting point in simulations. The exponential function used was the very best among thousands fitted by the commercial program TableCurve (version 4, Jandel Scientific Software). It also fits well similar data reported earlier in a paper by Bartolotta et al. (1993). In the concluding section of this paper we will estimate the inaccuracy of the simulation results due to a possible inaccuracy of this fit.

Table 2
EPR signals of test dosimeters irradiated and measured at SCRM

Target dose (Gy)	Replicate dosimeter #	Radiation signal amplitudes						
		Orient 1	Orient 2	Orient 3	Mean orient 1–3	RSD orient 1–3 (%)	Mean repl 1–9	RSD repl 1–9
0.5	1	0.504	0.520	0.610	0.544	10.5	0.509	5.6%
	2	0.450	0.514	0.459	0.474	7.3		
	3	0.501	0.547	0.575	0.541	6.9		
	4	0.456	0.549	0.549	0.518	10.3		
	5	0.523	0.393	0.541	0.486	16.6		
	6	0.579	0.551	0.479	0.536	9.6		
	7	0.501	0.560	0.496	0.519	6.8		
	8	0.540	0.404	0.544	0.496	16.0		
	9	0.485	0.475	0.452	0.471	3.6		
	Mean:	0.504	0.501	0.523				
	RSD (%):	7.9	12.7	10.4				
1.0	1	1.250	1.163	1.179	1.197	3.9	1.041	9.3%
	2	0.954	0.968	1.068	0.997	6.2		
	3	0.945	1.023	1.106	1.025	7.8		
	4	0.980	0.953	1.025	0.986	3.7		
	5	0.937	1.040	1.002	0.993	5.3		
	6	1.259	1.198	1.168	1.208	3.8		
	7	1.053	1.095	0.945	1.031	7.5		
	8	0.898	0.916	0.951	0.922	2.9		
	9	0.979	1.026	1.034	1.013	3.0		
	Mean:	1.028	1.043	1.053				
	RSD (%):	13.1	9.1	8.1				
2.0	1	1.974	2.139	2.110	2.074	4.2	2.086	1.7%
	2	2.166	2.192	1.999	2.119	4.9		
	3	1.940	2.050	2.069	2.020	3.4		
	4	2.085	2.133	2.002	2.073	3.2		
	5	2.062	2.101	2.075	2.079	1.0		
	6	2.037	2.110	2.031	2.059	2.1		
	7	2.031	2.217	2.032	2.093	5.1		
	8	2.089	2.148	2.142	2.126	1.5		
	9	2.099	2.142	2.158	2.133	1.4		
	Mean:	2.054	2.137	2.069				
	RSD (%):	3.3	2.3	2.8				
5.0	1	4.956	5.038	5.008	5.001	0.8	5.036	1.4%
	2	5.058	4.962	4.863	4.961	2.0		
	3	4.981	5.041	4.934	4.985	1.1		
	4	5.115	5.038	5.125	5.092	0.9		
	5	5.212	5.108	5.099	5.140	1.2		
	6	5.136	5.157	5.032	5.109	1.3		
	7	4.951	5.040	4.976	4.989	0.9		
	8	5.005	4.922	4.931	4.952	0.9		
	9	5.076	5.135	5.070	5.094	0.7		
	Mean:	5.067	5.050	5.004				
	RSD (%):	1.7	1.6	1.6				

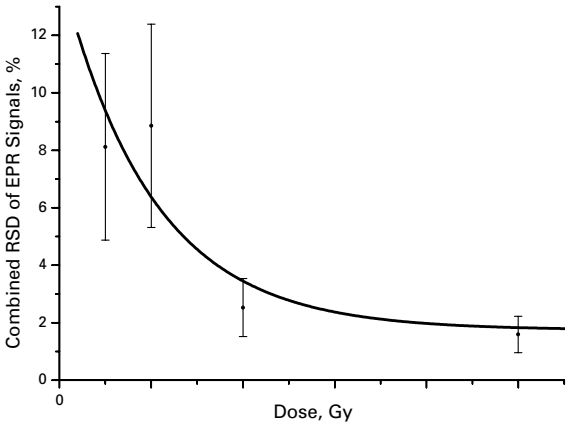

Fig. 5. Dependence of the relative standard deviation of signals of replicate dosimeters on the dose. The data were obtained by combining the results of Tables 1 and 2 for each dose (weighed averaging of the variances). The bars show 95% confidence intervals determined according to Natrella. The equation of the fit is $y = 1.748 + 12.61 \times \exp(-x)$.

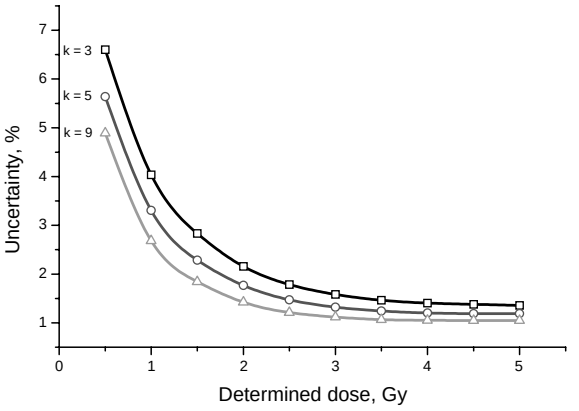

Fig. 6. Dependence of the uncertainty (1σ) in the dose determined with EPR alanine dosimetry in radiotherapy range on the dose. Calibration design: 4 calibration doses (0.5, 1, 2, and 5 Gy), four replicates for each dose; k is the number of replicate dosimeters per test dose.

The RSD of replicate signals does not reflect all of the potential sources of errors in Y values, and we have to address some other inaccuracies whose values could only be estimated (Type B uncertainties). Environmental effects should normally be corrected for using the data on alanine signal fading at various humidities (Sleptchonok et al., 2000). This correction may not be quite perfect, though, and a 0.2% error on average is assumed from that source. During the calibration session, the sample tube gets slightly contaminated with irradiated alanine powder, which may result in a 0.1% error for some dosimeters. The variations in the spectrometer sensitivity should typically be monitored with an adjacent reference sample, but, as the reference signal is not recorded simultaneously with the alanine signal, a 0.2% error may occur from the sensitivity change between the recordings (Nagy et al., 2000b). Summed up in quadrature, these give 0.3% as the value that should be added (also in quadrature) to the RSD value for each dose evaluated from Fig. 5.

Uncertainties in X stem from the nonuniformity of the radiation field of the calibration source, uncontrollable variations in irradiation temperature, source timer errors, and the very small inaccuracy in evaluation of the dose rate at the period of irradiation due to radionuclide decay. Radiation field nonuniformity and reproducibility of sample positioning in the source may vary significantly depending on the quality of the calibration source. A somewhat conservative estimate of 0.1% is assigned to high metrological-quality calibration sources. To conform to the low-dose rate of the medical source, short irradiation times often have to be used on calibration sources, which typically have higher dose rates. A one-second error in measuring a 10-min time period is just below 0.2%. The temperature of irradiation should be controlled and the appropriate correction (Nagy et al., 2000a) should be applied. Here, this is 0.2%. The decay correction is much smaller than the corrections discussed above and usually can be neglected. Summed in quadrature, the uncertainty in X is 0.3%. The uncertainty in the dose rate of the calibration source is not included here. An error in the dose rate produces a bias in all the X values in the same direction by a constant (although unknown) value and, therefore, is unrelated to the generated deviations, which are random in direction and size. The total uncertainty of a dose determined by transfer dosimetry should be obtained by summing, in quadrature, the uncertainty produced by the Monte Carlo simulation and the uncertainty of the calibration source dose rate.

Thus, in addition to the Y variance increase with dose by a complicated law, the X variance is neither zero nor constant. Obviously, the classic least-squares technique, which is based on the assumption of data homoscedastisity and zero uncertainty in X (Draper and Smith, 1981) is not applicable in this case, and Williamson's technique should be employed.

Fig. 6 shows the total uncertainties (1σ) of dose transfer for the calibration design used to produce the signals shown in Tables 1 and 2. For a 1.5 Gy dose and higher, uncertainty within 2% can be attained. For doses 2.5 Gy as few as three replicate dosimeters are required for each test dose. This is the uncertainty of the dose transfer only, and the total uncertainty of the determined dose can be obtained by combining it, in

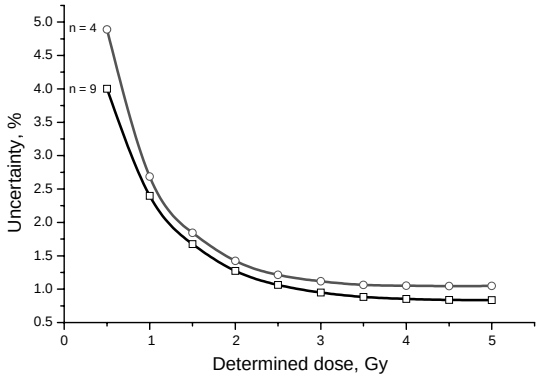

Fig. 7. Uncertainties (1σ) in the doses determined with EPR alanine dosimetry in the radiotherapy range at 4 and 9 replicate dosimeters for each calibration dose. Calibration doses: 0.5, 1, 2, and 5 Gy, nine replicate dosimeters for each test dose.

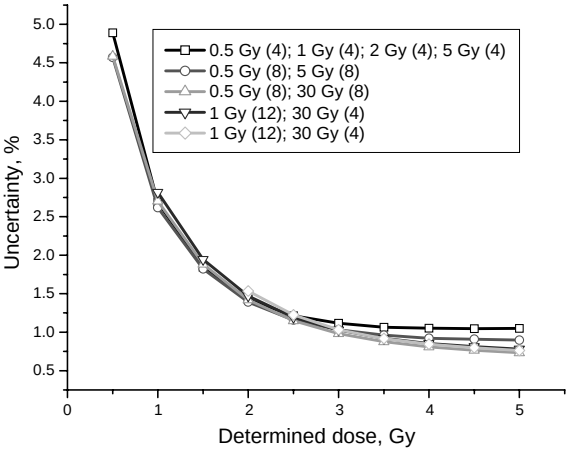

Fig. 8. Uncertainties (1σ) in the doses determined with EPR alanine dosimetry in the radiotherapy range at various calibration designs. The number in parentheses shows the number of replicate dosimeters in each calibration dose. Nine replicate dosimeters for each test dose are assumed.

quadrature, with the uncertainty of the dose rate of the reference radiation source.

Fig. 7 shows what decrease in uncertainty could be achieved if nine, instead of four, replicate dosimeters were used for each calibration dose. As predicted by the regression theory, the difference is the smallest in the area of the regression centroid, where the uncertainty in the plot is the smallest, increasing to both ends of the calibration range. It can be seen that, in the dose range (1.5–3) Gy (which is probably the most practical from the viewpoint of maximum precision in minimal time), increasing the time and labor by a factor of more than two for measuring nine calibration replicates for each dose instead of four results only in a negligible decrease in the uncertainty. Obviously, in the low-dose range, with its slow signal registration, this approach would not be prudent.

Fig. 8 demonstrates what uncertainty improvement can be attained by optimizing the values of the calibration doses. For a classic lineal regression (with zero variance in X and constant variance in Y), the uncertainty in X determined from Y, decreases significantly when all the calibration points are located at the edges of the calibration range (Ott and Myers, 1968). It can also be readily deduced from the basic regression equations (Draper and Smith, 1981) that when the X value of the upper edge is much larger than the X value of the lower edge, an even distribution of the points is optimal. In our case, though, the improvement in precision resulting from such change in the design is very small and noticeable mostly in high-dose area of the calibration range. This is understandable, because the displacement of the calibration points to the edges of the calibration range effectively puts as many as half of them into the area of the extremely large scatter, and this significantly diminishes the theoretically predicted gains from the edge-point design. The expansion of the calibration range to 0.5–30 Gy, which also normally improves the precision significantly in the case of the classic regression, does not provide much improvement (a more detailed explanation why the edge-point design with a wide calibration range usually helps improve the precision can be found in the paper by Nagy, 2000). Again, in our case, a large uncertainty in the low-dose end of the calibration line effectively negates any gains of the much wider calibration range, and the only benefit of this design is the possibility to record the spectra of the dosimeters irradiated to the higher dose much faster.

Table 3
Results of SCRM Source calibration in the radiotherapy dose range

Test vial no.	Determined dose (Gy)	Real dose[a] (Gy)	Difference (%)
1	0.509	0.526	3.2
2	1.041	1.052	1.0
3	2.086	2.095	0.4
4	5.036	5.102	1.3

[a] Calculated from the dose rate provided by the NIST official dose certification service.

3.4. Calibration of the SCRM source in the low-dose range

Table 3 shows the results of the low-dose calibration of the source on the basis of the data presented in Table 1 and 2. It can be seen that the determined doses are well within the uncertainties predicted for this degree of

signal scatter by Monte Carlo calculations. This is not unexpected, because, as mentioned several times above, at Gaussian and similar distributions, the random values close to the true value are far more probable than those located farther on the extremes, and small statistical samples never can provide true information about the real degree of scatter. If many more than four doses were determined, and with more than a single calibration plot, much larger discrepancies would be observed in some cases, and the variance calculated on the basis of all of them would be much closer to the values predicted by the simulation experiments. The relatively high deviation for the highest dose is indicative of the random nature of these numbers.

4. Conclusions

This study demonstrates that alanine dosimetry can provide an acceptable accuracy in the dose range (1.5–5) Gy that may be applied to many radiotherapy applications without unreasonable time and labor expenses. The precipitous decrease in uncertainty over the (0.5–2.0) Gy range (Fig. 6) suggests that operating in the (2–3) Gy range is preferred, if possible.

Unlike in the papers by the other authors, an attempt was made to estimate the *overall* uncertainty of the dose transfer in the (0.5–5) Gy range. An important question is how these results are transferable. Commercially available dosimeters and an EPR spectrometer, whose sensitivity, at this time, is representative of the majority of the instruments used in EPR dosimetry were intentionally used. If these dosimeters are used, the spectrometer is of the same class, and the user reproduces this technique, very similar uncertainties should be expected. The only point that remains unclear is how accurately the various contributions to the uncertainties in X and Y that were put into the model have been estimated. As a test, some simulations were repeated with an overly conservative estimate of the dependence of RSD on the dose (Fig. 5), namely, the fit of the upper ends of the confidence intervals for RSD as used. The uncertainties obtained with this approach were about one-quarter higher than the uncertainties shown in Figs. 6–8. As the other, B Type, contributions were significantly smaller, inaccuracies in them will not produce a significant change in the value obtained by summing in quadrature.

Comparison of the signal scatter of replicate dosimeters measured in this study with similar data available in the literature did not reveal large differences, although the main reason for scatter in the other studies was sometimes different. This suggests that the data reported in this paper may be used as a very rough estimate of the uncertainties that may be expected in calibrations with dosimeters of a different type.

As in previous papers (Sleptchonok et al., 2000; Nagy et al., 2000a), the goal is not so much to report the exact numbers, but the method for their production. Unfortunately, EPR dosimetry trails far behind most of the analytical sciences in the culture of reporting its performance characteristics and, in particular, uncertainty. It is hoped that this paper forms a foundation for progress in that direction.

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