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An update on “dose calibrator” settings for nuclides used in nuclear medicine

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Abstract

Most clinical measurements of radioactivity, whether for therapeutic or imaging nuclides, rely on commercial reentrant ionization chambers (“dose calibrators”). The National Institute of Standards and Technology (NIST) maintains a battery of representative calibrators and works to link calibration settings (“dial settings”) to primary radioactivity standards. Here, we provide a summary of NIST-determined dial settings for 22 radionuclides, including several previously unreported settings. In general, current manufacturer-provided calibration settings give activities that agree with NIST standards to within a few percent.

Keywords

radioactivity standards; quantitative imaging; secondary standards; calibration factor; dial setting; dose calibrator; ionization chamber

1. Introduction

Activity measurements in the radiopharmaceutical industry rely almost exclusively on commercial reentrant ionization chambers referred to variously as “radionuclide calibrators”, “activimeters”, or “dose calibrators”. These devices, consisting of a pressurized ionization chamber and an electrometer, typically provide a readout directly in activity units, relying on a specific calibration setting or “dial setting” (DS) to convert measured current to displayed activity. In 2000, Zimmerman and Cessna reported on the methodology and results of experiments at the National Institute of Standards and Technology (NIST) to determine DSs for 11 radionuclides commonly used in nuclear medicine applications [1]. In this letter, we update those results to include new imaging and therapeutic radionuclides. We provide appropriate references, where available, and briefly describe the measurements where the determinations are otherwise unpublished.

Disclaimer: Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation 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.

2. Methods

In most cases, dial setting determinations are carried out using the calibration curve method [1]. A source is measured at a series of DSs covering a range that includes the setting that returns the true activity. One advantage of this method is that it can be employed prior to a precision assay of the radioactive source as long as an approximate activity can be determined to select an appropriate range of DSs for the curve. Another advantage is that this method makes it easier to evaluate uncertainties since the standard error of the fit (calculated from the residuals of the fit to the calibration curve) provides a good estimate for the uncertainty due to the method and the sensitivity to small changes in DS. This approach also allows the uncertainty to be expressed in terms of both DS units and activity.

Uncertainties on determined DSs or, analogously, on the activities measured with them are typically mostly due to the uncertainty on the primary standard. Primary activity measurements are performed at NIST using a variety of techniques, among which coincidence counting [2,3] and liquid scintillation-based efficiency tracing or triple-to-double coincidence ratio (TDCR) counting [4,5] are most common. For radionuclides detected with high counting efficiency and relatively simple decay schemes, total combined uncertainties—determined using the methodology outlined by Taylor and Kuyatt [6]—on the order of 0.5 % are often achievable. With these standards, a dose calibrator can typically be calibrated to allow activity measurements with expanded ($k = 2$) uncertainties on the order of 1 %.

3. Results and Discussion

Table 1 provides NIST-determined dial settings and uncertainties for 22 radionuclides. For some nuclides, DSs are given for multiple geometries. The table points to relevant references for each DS.

In most cases, the settings reported here match those given in the previous NIST summary [1]. The very notable exception is for ^{18}F . The settings reported here supplant the earlier ones, reflecting the revised NIST standard [7,21]. Another exception is for $^{117\text{m}}\text{Sn}$, where Table 1 gives a value calculated by averaging the results of determinations performed with two different solution compositions. The determination for ^{153}Sm has been updated based on new measurements, but differs only slightly from the earlier report.

In most cases, new DS determinations have been described in the literature. The few exceptions are addressed here:

$^{99\text{m}}\text{Tc}$

In November 2017, a standard NIST 5 mL flame-sealed ampoule containing 5 g of solution was obtained from the NIST Radioactivity Measurement Assurance Program (NRMAP) [22] and measured on multiple dose calibrators. The standard activity was taken from secondary standard ionization chamber (SSIC) measurements on NIST Chamber “A” (ICA) [23] using the calibration factor (“ K -value”) determined in 1976 [24]. The primary standardization used coincidence counting with a pressurized proportional counter/NaI(Tl) system. The

uncertainty on the standard activity (0.44 %) was the largest component in the combined standard uncertainties on the DSs.

The manufacturer-recommended DS (= 80) for the Capintec (Ramsey, NJ) CRC-15R and CRC-35R chambers resulted in activity readings biased by +1.6 % and +1.9 %, respectively [25].¹ The recommended DS (= 37.1) for the AtomLab-400 and AtomLab-500 chambers (manufactured by Sun Nuclear; Shirley, NY) resulted in readings biased by -1.6 % and -2.1 %, respectively [26].²

Source geometry sensitivity in dose calibrator measurements of ^{99m}Tc has been discussed previously [27] and in reference [1], DSs for the CRC-12 were given for the ampoule and 10 mL Mallinckrodt dose vial geometries. Those values are preserved in Table 1. Significantly, the new values presented for the CRC-15R and CRC-35R are consistent with the prior DS found for the CRC-12.

¹¹¹In

In September 2012, four ampoules from the NRMAP were measured on multiple dose calibrators. The standard activity was taken from ICA using the *K*-value determined in 1977. The primary standardization used coincidence counting with a pressurized proportional counter/NaI(Tl) system. The uncertainty on the standard activity (0.55 %) was the largest component in the total combined uncertainties on the DSs.

The manufacturer-recommended DS (= 303) for the CRC-12, CRC-15R, and CRC-35R chambers [25] resulted in activity readings biased by +3.2 %, +3.4 %, and +2.4 %, respectively.

¹⁵³Sm

In July and August 2013, an ampoule from the NRMAP was measured on multiple dose calibrators. The standard activity was taken from ICA using the *K*-value determined in 1985. The primary standardization used 4 $\pi\beta$ liquid scintillation counting. The primary standard had a fairly large uncertainty (≈ 2 %) and a large correction (≈ 1.5 %) for the geometric drift in ICA [28] was required; a new primary standardization for this nuclide is desirable. The uncertainty on the standard activity (≈ 2 %) was the largest contributor to the combined standard uncertainties on the DSs.

For the Vinten 671 Ionization Chamber (VIC) [29] measurements, impurity corrections for ¹⁵⁴Eu and ¹⁵⁶Eu were based on HPGe measurements and volume-corrected IC responses communicated to us by the National Physical Laboratory (NPL; United Kingdom) [30]. The NIST- and NPL-determined calibration factors agreed to within ≈ 0.2 %. For the dose calibrators, impurity corrections could not be made since ¹⁵⁴Eu and ¹⁵⁶Eu responses at the ¹⁵³Sm DS were not known. Over time, the effect of ingrowing impurities on DS bias was

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²While each calibrator has its own manual, the DS tables are consistent across the Capintec R series and across the Biodex AtomLab series. We cite just one manual from each manufacturer

evident. To reduce bias, DS determinations relied on the earliest data acquired, where they appeared stable to $< 0.1\%$. The large uncertainties due to the standard activity and height correction dwarf any residual biases or underestimate of the total combined standard uncertainties.

^{177}Lu

In 2012, NIST participated in a comparison of clinical dose calibrator measurements of ^{177}Lu piloted by the NPL [31]. The source was delivered in a 10 mL Schott-type dose vial and NIST performed measurements on multiple dose calibrators in both the dose vial and 5 mL ampoule geometries. The standard activity was taken from ICA using the K -value determined in 2009 by anticoincidence counting [32]. The uncertainty on the standard activity (0.37 %) was the largest component in the combined standard uncertainties on the determined DSs in all cases except for the CRC-35R calibrator where the uncertainty on the reading (estimated in this case from the range of minimum and maximum readings observed over a few seconds) was larger.

In general, the results were in good agreement with the manufacturer's recommendations, with previous NIST-determined DSs [33], and with the NPL.

4. Discussion

Ionization chamber calibrations are an integral part of primary activity standardization efforts at NIST. For the short-lived radionuclides of interest in nuclear medicine especially, calibrated ionization chambers establish an enduring means of assaying new samples with traceability to the primary activity standard. As SSCs like the VIC establish indirect links with other metrology institutes around the world, dose calibrators link NIST standards to clinical and industrial measurements—with some caveats.

NIST always recommends that DS determinations are considered valid only for the specific calibrators and source characteristics described. Users should verify the results on their own systems. This is especially important when environmental conditions (e.g., backgrounds, local shielding) may significantly differ from those at NIST. Using the NIST *methods* rather than the NIST *results* also ensures against any larger than expected calibrator-to-calibrator variation.

In addition to suggesting that users verify all calibrations on their own instruments, NIST stresses the importance of regular quality control measurements (see user's manuals), especially measurements of a long-lived source to monitor response constancy. Long-term trending in constancy measurements or abrupt deviations from the expected response require investigation. At best, a change in response, perhaps owing to a change in the local environment (e.g., addition of shielding) indicates that new calibration verifications are required. A change in response that cannot be explained by a change in the local environment may indicate instrument failure (e.g., damage to the electronics or a loss of chamber pressure), requiring that the calibrator be removed from service.

Another important consideration involves the practice of “sharing” calibrations between instruments. This practice is common when a user maintains multiple calibrators of the same type: one calibration verification on a specific instrument serves to establish a site-specific DS which is then shared among all instruments. This practice can be dangerous if a DS is shared between instruments from the same manufacturer but from different generations. For example, the Capintec CRC-12, CRC-15R, and CRC-35R calibrators maintained at NIST are designed to give similar responses for a given DS; however, the CRC-25PET is representative of a different series of instruments designed to handle higher activities for positron emission tomography (PET) applications, and requires a distinct DS. In fact, the CRC-25PET manual [34] includes DSs for only eight nuclides, half of which were determined with NIST-traceable sources and the other half by inter-comparison with a CRC-15R instrument. The validity of a DS should always be tested for each individual calibrator.

Occasionally, updated standards or nuclear data evaluations (see, for example, [9, 19]) result in a change in the DS recommended by instrument manufacturers or pharmaceutical companies. DS changes should only be made in response to specific instructions from pharmaceutical manufacturers, and any discrepancy between a local assay and the activity reported by the manufacturer should be investigated.

Finally, in recent years the use of long-lived calibration surrogates for some radionuclides has become a viable option. The use of ^{68}Ge sources as surrogates for short-lived positron emission tomography (PET) radionuclides is now firmly established [9, 35]. However, some approaches, such as the use of ^{133}Ba as a surrogate for ^{131}I can lead to errors [15].

5. Conclusions

NIST has carried out calibrations for 22 radionuclides on different reentrant ionization chambers (“dose calibrators”) and often in multiple geometries. In most cases, calibration factors or “dial settings” (DS) are determined using the calibration curve method. This paper presents a collection of NIST-determined DSs for medically relevant radionuclides, addressing uncertainties and pointing to relevant references. The DSs are considered applicable for the NIST calibrators and the specifically described geometries; users are encouraged to check their validity on their own systems.

In general, the NIST-determined DSs are consistent with current manufacturer recommendations. This is in contrast to the situation reported in 2000 [1], when most of the considered manufacturer-provided DSs overestimated activities, in some cases by more than 20 %. In general, improved accuracy can be interpreted as reflecting the positive impact of an emphasis on traceability to common measurement standards.

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Table 1

NIST-determined calibration factors in $\text{pA}\cdot\text{MBq}^{-1}$ for the Vinten 671 Ionization Chamber (VIC) or as dial settings (DSs) for Capintec or Biodex calibrators. The calibration factors with their expanded ($k=2$) uncertainties are given in bold in each specific radionuclide and geometry. The standard geometry, denoted simply as “ampoule” in the table, is the NIST 5 mL flame-sealed ampoule containing 5 mL of radioactive solution. Below each calibration factor, the % uncertainty on the measured activity that results from the expanded uncertainty on the calibration factor ($U_A / \%$) is given. The year of the NIST primary standardization upon which the DS determination is based is given, along with the reference describing the DS determination, where available. In some cases, the DS is given with a multiplier, e.g., “57(2) X 10”, indicating that the reading using DS = 57 should be multiplied by 10 to give the correct activity; in this example the expanded uncertainty on the DS is ± 2 DS units.

Nuclide	1 st std	Ref.	Geometry	Instrument					
				VIC / $\text{pA}\cdot\text{MBq}^{-1}$	CRC-12	CRC-15R	CRC-25PET	CRC-35R	AL-400 AL-500
F-18 in % Activity	2012	[7]	ampoule	10.36(8)	450(5)	449(4)	455(4)	450(4)	
				0.8	1.0	0.7	0.7	0.7	
Cu-62 in % Activity	1999	[1]	ampoule	489(8)					
				1.4					
Cu-62 in % Activity	1999	[1]	35 mL syringe	499(6)					
				0.8					
Cu-64 in % Activity	2016	[8]	ampoule	1.952(29)	118(2) X 2	135(2) X 2	119(2) X 2	53.7(7)	54.0(8)
				1.5	1.2	1.3	1.9	1.4	1.4
Ge-68 in % Activity	2008	[9]	ampoule	10.04(9)	440(5)	440(7)	448(4)	442(4)	10.1(1)
				0.9	1.0	1.4	0.7	0.8	0.9
Ge-68 in % Activity	2008	[9]	3 mL epoxy in a mock 6 mL syringe	10.00(10)	453(7)	436(5)	451(5)	447(9)	10.1(1)
				1.0	1.2	1.0	1.0	1.7	1.0
Ge-68 in % Activity	2008		6 mL cylindrical phantom insert	10.12(10)					
				1.0					
Y-90 in % Activity	1993	[10]	Anpoule ¹		48 X 10	48 X 10		48 X 10	

Nuclide	1 ^o std	Ref.	Geometry	VIC / pA·MBq ⁻¹	Instrument					
					CRC-12	CRC-15R	CRC-25PET	CRC-35R	AL-400	AL-500
Y-90 in % Activity	1993	[11]	10 mL syringe with 3 to 9 mL-YCl ₃		57(2) X 10	55(2) X 10		54(2) X 10		
Tc-99m in % Activity	1976	[1]	ampoule	1.247(11) 0.9	82	81(2) 0.9	91(2) 0.9	81(2) 0.9	37.7(3) 0.9	37.9(3) 0.9
Tc-99m in % Activity	1976	[1]	10 mL Mallinckrodt dose vial		78					
In-111 in % Activity	1977		ampoule	4.081(50) 1.2	316(5) 1.3	315(5) 1.2	323(5) 1.3	313(5) 1.2	13.6(2) 1.2	13.3(2) 1.3
Sn-117m in % Activity	1998	[12]	3.5 mL dose vial ²		133(6)					
I-123 in % Activity	1976	[13]	ampoule	1.758(18) 1.0	306(4) 1.4	306(4) 1.4	321(4) 1.4	297(4) 1.3	13.2(1) 1.4	13.0(1) 1.4
I-125 in % Activity	1989	[1]	ampoule ³		313					
I-131 in % Activity	1978	[15]	ampoule ⁴	3.993(36) 0.90	156(2) 0.90	156(4) 0.90	174(4) 0.90	158(4) 0.90		
Ba-133 in % Activity	1983	[15]	ampoule ⁴	4.287(59) 1.4	628(2) 1.4	626(3) 1.4	640(2) 1.4	618(2) 1.4		
Xe-133 in % Activity	1988	[1]	ampoule		184					
Xe-133 in % Activity	1988	[1]	3 mL Dupont dose vial		181					

Nuclide	1 ^{std}	Ref.	Geometry	VIC / pA·MBq ⁻¹	Instrument				
					CRC-12	CRC-15R	CRC-25PET	CRC-35R	AL-400 AL-500
Gd-153 in % Activity	1989	[1]	ampoule		545				
Sm-153 in % Activity	1985		ampoule ⁵	0.656(28) 4.2	248(7) 2.1	250(7) 2.1	276(7) 2.1	248(7) 2.1	16.8(4) 2.1 16.5(4) 2.1
Ho-166 in % Activity	1991	[16]	ampoule		683(7) X 10			691(8) X 10	
Ho-166 in % Activity	1991	[16]	16 mL in 20 mL glass dose vial		672(11) X 10			678(19) X 10	
Ho-166 in % Activity	1991	[16]	10 mL plastic dose vial		703(8) X 10			712(4) X 10	
Lu-177 in % Activity	2009		ampoule ⁶	0.344(3) 0.76	451(5) X 10 1.0	449(5) X 10 0.9	435(5) X 10 1.0	450(8) X 10 1.5	
Re-186 in % Activity	1989	[1]	ampoule		480 X 10				
Re-186 in % Activity	2000	[17]	Ace Glass v-vial, 0.96 g to 2.12 g ⁷		447(2) X 10 0.4				
Re-186 in % Activity	2000	[17]	Wheaton v-vials, 1.0 g to 2.2 g ⁷		462(2) X 10 0.7				
Re-188 in % Activity	1999	[18]	ampoule ⁸		631(4) X 10 0.4				
Re-188 in % Activity	1999	[18]	5 mL SoloPak dose vial, 2 mL ⁸		621(3) X 10 0.4				

Nuclide	1 ^o std	Ref.	Geometry	Instrument					
				VIC / pA·MBq ⁻¹	CRC-12	CRC-15R	CRC-25PET	CRC-35R	AL-400 AL-500
W-188 in % Activity	2002	[19]	ampoule ⁹	0.595(11) 1.8					
Ra-223 in % Activity	2013	[20]	ampoule	3.171(40) 1.2		233(2) 0.65	234(2) 0.75	234(4) 1.1	19.0(2) 0.87 18.7(2) 0.87
Ra-223 in % Activity	2013	[20]	ampoule	3.18(2) 0.63	231(5) 1.6	231(6) 1.9		234(5) 1.6	
Ra-223 in % Activity	2013	[20]	20 mL dose vial	3.19(4) 1.3	229(5) 1.6	231(5) 1.6		234(5) 1.6	
Ra-223 in % Activity	2013	[20]	2 mL syringe ¹⁰	3.31(6) 1.8	237(8) 2.5	232(7) 2.2		234(7) 2.2	

¹Reference [10] also gives DSs for several v-vial geometries; no uncertainties given.²The value and accompanying uncertainty reported here are the average and standard deviation of two determinations performed on solutions with different compositions.³See also [14] for volume effects and v-vial geometries.⁴The DSs reported here were determined by the “dialing-in” method [1], where the DS is tuned to give the correct activity. Uncertainties are estimated as equivalent to the uncertainty on the activity determined with the contemporaneously-determined KV[C].⁵The primary standard has a 2 % combined standard uncertainty; Zimmerman and Cessna found DS = 252 for the CRC-12 chamber in 2000 [1].⁶This DS was also found to be valid for a 10R Schott vial.⁷Reference [17] also gives a formula for volume dependence over a wider range.⁸See also [19] for recommendations on measuring mixed W-188/Re-188 solutions.⁹Reference [19] also gives correction factors for Capintec readings at manufacturer-recommended settings.¹⁰Reference [20] also gives results for 5 mL and 20 mL syringes with several total solution volumes.