(Mis)use of ^{133}Ba as a calibration surrogate for ^{131}I in clinical activity calibrators

B. E. Zimmerman and D. E. Bergeron

Physical Measurement Laboratory, National Institute of Standards and Technology
Gaithersburg, MD 20899-8462 USA

ABSTRACT

Using NIST-calibrated solutions of ^{131}Ba and ^{131}I in the 5 mL NIST ampoule geometry, measurements were made in three NIST-maintained Capintec activity calibrators and the NIST Vinten 671 ionization chamber to evaluate the suitability of using ^{133}Ba as a calibration surrogate for ^{131}I. For the Capintec calibrators, the ^{133}Ba response was a factor of about 300% higher than that of the same amount of ^{131}I. For the Vinten 671, the Ba-133 response was about 7 % higher than that of ^{131}I. These results demonstrate that ^{133}Ba is a poor surrogate for ^{131}I. New calibration factors for these radionuclides in the ampoule geometry for the Vinten 671 and Capintec activity calibrators were also determined.

Keywords: activity calibrators, barium-133, iodine-131, ionization chambers

1. Introduction

Iodine-131 is one of the most commonly used radionuclides in nuclear medicine, particularly in the developing world. Clinical applications include Na[^{131}I] for diagnosing and treating thyroid disease, both malignant and benign (Sawka, *et al*. 2009; Ross 2011) ^{131}I meta-iodobenzylguanidine (mIBG) for neuroendrocrine tumors (Riad 2011); ^{131}I-ethiodized oil for hepatocellular carcinoma (Ahmadzadehfar, *et al.* 2011); and radiolabeled monoclonal antibodies for non-Hodgkins lymphoma (Calais and Turner 2012). Measurements of ^{131}I prior to administration are usually made in the hospital or radiopharmacy using activity calibrators (commonly called “dose calibrators”). A traceable calibration for the activity calibrator is crucial for ensuring the accuracy of the dosage prior to administration.

Although most guidance documents, including those from the International Atomic Energy Agency (IAEA) (2006), standards groups (ANSI 2004), and professional societies (AAPM 2012), recommend that activity calibrators be directly calibrated against standards of the same radionuclide, the expense and limited availability of ^{131}I standard solutions force some clinics, particularly in (but not limited to) developing countries, to use surrogate sources instead. The lack of direct prohibition against this practice in some regulatory documents (CNSC 2006) may even appear to give tacit approval for this practice.

The long half-life (10.540(6) a) and photon spectrum of ^{133}Ba (DDEP 2015) make it attractive for use as a surrogate, especially since many locations also utilize ^{133}Ba check sources as part of their Quality Assurance measurements for constancy and may already have a source on hand. The main photon energies (≈ 360 keV) and total photon energies per decay are about the same for both radionuclides. These properties make ^{133}Ba an especially interesting surrogate for ^{131}I in physics studies for single photon emission computed tomography (SPECT) imaging, and in fact a set of calibrated ^{133}Ba sources has been successfully used in a recent international single photon emission computed tomography SPECT image quantification comparison organized by the IAEA (Zimmerman, *et al.* 2013).

However, the fact that ^{131}I decays via β particle emission (and therefore will also produce bremsstrahlung) and ^{133}Ba undergoes electron capture (which results in substantial differences in x ray emission), as well as the presence of higher energy photons in the ^{131}I decay scheme, means that activity calibrators will have very different responses for the same amount of activity of each radionuclide. Geometrical effects can also introduce significant differences in activity calibrator response for these radionuclides, especially when calibrations are made with solid check sources (in common use clinically) when the main measurement geometry is a liquid in a syringe or vial.

Attempts have been made by manufacturers to compensate for differences between the two decay schemes by introducing surrogate sources that use a combination of radionuclides (such as ^{133}Ba and ^{137}Cs), but differences in the half-lives of the radionuclides will cause their activity ratio to change over time, requiring additional corrections to be made.

This work was carried out to quantify the relative responses between standardized sources of ^{133}Ba and ^{131}I in several clinical activity calibrator models in an attempt to demonstrate the inappropriateness of using ^{133}Ba as a surrogate for calibrating activity calibrators.

2. Materials and Methods

During the experiments described in Zimmerman, *et al.* (2013), four 5 mL NIST ampoules were prepared, each containing nominally 4.4 MBq·g^{-1} of ^{133}Ba in 5 g of a carrier solution of 5 mmol·L^{-1} $BaCl_2$ in 0.5 mol·L^{-1} HCl. Two of those ampoules, denoted Ba-D1-A3 and Ba-D1-A4, were also used in the present study (the solutions from the other two ampoules were used in experiments not related to this study). The total ^{133}Ba activities for Ba-D1-A3 and Ba-D1-A4 were calibrated by measurement in NIST "4π"γ ionization chamber "A" (IC "A") as previously described (Zimmerman, *et al.* 2013) and found to be 22.57(15) MBq and 20.01(13) MBq at the reference time, respectively. The uncertainties are the combined standard uncertainties on the IC "A" measurements calculated as described in Zimmerman *et al.* (2013).

For the ^{131}I measurements, a single NIST 5 mL ampoule containing Standard Reference Material 4401L-7, Lot 38 (NIST 2012) was used. This solution consisted of nominally 156 μg of KI, 0.234 μg of LiOH, and 70 μg Na_2SO_3 per gram of solution in distilled water. The activity of the solution was calibrated in IC "A" and found to be 24.34(11) MBq at the reference time. The uncertainty on the activity value is the combined standard uncertainty calculated from the quadratic addition of components due primarily to the IC "A"

calibration factor (0.44 %), measurement precision (0.06 %), live-time determination (0.05 %), radium reference source positioning (0.05 %), and mass measurements (0.05 %).

Each of the ^{133}Ba ampoules was measured in 4 commercial activity calibrators maintained at NIST: a Capintec CRC-15R, a Capintec CRC-12, a Capintec CRC-25R, and a Vinten 671 connected to a Keithley 6517 electrometer (the system is denoted hereafter as "VIC") [1]. The Capintec activity calibrator measurements were made with the ampoule in the bottom of the standard dipper that shipped with each chamber at both the "^{131}I" and "^{133}Ba" dial settings recommended by the manufacturer, which are 151 and 591, respectively. The Capintec CRC-12 had been modified by the manufacturer to allow for direct current readings in addition to operating in its "normal" mode. For the VIC measurements, the vial holder was used with the ampoule sitting in the lowest position.

A total of 100 measurements of the ionization current were taken in the VIC at intervals of 2 seconds for each ampoule; 1000 measurements of the background current were made before and after the ampoule measurements. The ^{131}I ampoule was measured in each chamber in the same manner as was done for the ^{133}Ba ampoules, except that the measurements were carried out only at the manufacturer's recommended setting for ^{131}I in the case of measurements made in the Capintec chambers.

For both radionuclides, the dial setting for the ampoules in each of the Capintec chambers was re-determined by changing the dial until the correct total activity was displayed on the readout.

[1] 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.

3. Results and Discussion

For the VIC, the calibration coefficients for the ^{131}I and ^{133}Ba in ampoules were measured to be 3.993(18) pA·MBq^{-1} and 4.287(30) pA·MBq^{-1}, respectively, giving a ^{133}Ba:^{131}I response ratio of 1.074(9). The uncertainties on the individual calibration coefficients are combined standard uncertainties calculated from components due to decay correction (0.045 % and 0.004 % for ^{133}Ba and ^{131}I, respectively), the uncertainty on the ^{133}Ba and ^{131}I activity calibrations (0.66 % and 0.45 %, respectively), and repeatability of the ionization current measurements (0.3 % and 0.03 % for ^{133}Ba and ^{131}I, respectively). The large difference between the decay correction uncertainties originates from the differences in time between when the particular samples were calibrated and the time of the measurements made in this study. The ^{133}Ba solutions were calibrated well before these studies were performed, while the ^{131}I solution was calibrated within one to two days of the experiments. The ^{133}Ba calibration coefficient uncertainty also contains an additional component with magnitude 0.2 % to account for measurement variability between the two ampoules that is estimated from the standard deviation on the mean value of the calibration coefficients obtained from the two ampoules.

The value of 1.074(9) for the ratio of the ^{133}Ba and ^{131}I VIC calibration coefficients obtained in this study for the NIST standard 5 mL ampoule is in agreement with the ratio of 1.066(8) obtained from the volume- (or more correctly, mass) corrected calibration coefficients published by the National Physical Laboratory (NPL) for the 5 mL British Standard ampoule (Keightley 2012). Although minor differences exist between the configurations of the two ampoules (BSI 1983, NIST 2012), this level of agreement gives confidence in the present result. Further confidence can be gained by calculating the average photon energy per decay for each radionuclide. Based on the available decay scheme data (DDEP 2015) we obtain values of 376.1(19) keV per decay for ^{131}I and 398.2(11) keV per decay for ^{133}Ba, which gives a ratio of 1.059(6), which is in accord with the values given above to within uncertainties, assuming that

the VIC response to those average decay energies is nominally equal. The agreement between the three ratios also suggests that for the VIC, the contribution to the response from bremsstrahlung in the decay of ^{131}I is small, since otherwise a larger difference between the experimental NIST and NPL ratios and the one calculated solely from the photons would be observed.

The physical construction of the Capintec chambers and the VIC are quite different, namely the filling gas is at a higher pressure in the Capintec chambers and is nominally 1.22 MPa of argon instead of 1 MPa of nitrogen. As a result, the walls of the chamber are thicker in the Capintec calibrators in order to accommodate the higher pressure. The walls of the Capintec chambers are constructed from steel, whereas the Vinten chamber walls are aluminum. This will result in a different bremsstrahlung spectrum in each case. In addition, the outer walls of the Capintec calibrators contain additional shielding, as they are designed primarily to be used in radiopharmacies with relatively high levels of activity. The VIC, on the other hand, was designed to be a secondary standard instrument with emphasis on sensitivity at low energy and no additional shielding. This philosophy is also reflected in the inner wall construction, which results in a lower cutoff energy for the Vinten. Thus, it is expected that some differences in the relative responses for ^{133}Ba and ^{131}I between the chambers are observed.

By reading the current from the Capintec CRC-12 chamber, we can derive calibration coefficients for both radionuclides in a similar manner as for the VIC. For this instrument, we obtain values of 11.01(8) pA·MBq^{-1} and 3.76(2) pA·MBq^{-1} for the ^{133}Ba and ^{131}I ampoules, respectively. The uncertainties are standard uncertainties and were calculated from the components due to decay correction (0.045 % and 0.004 % for ^{133}Ba and ^{131}I, respectively), the uncertainty on the ^{133}Ba and ^{131}I activity calibrations (0.66 % and 0.45 %, respectively), and for ^{133}Ba, between ampoule measurement variability (0.2 %). This gives a ratio of 2.93(3) for the calibration coefficients measured in this particular chamber.

The activities reported by the various Capintec activity calibrators when measuring the ^{133}Ba and ^{131}I ampoules at the manufacturer's recommended settings for ^{131}I, are given in Table 1. As can be seen in the first column, the activities reported by the activity calibrators for ^{133}Ba are consistently a factor of 3 higher than the calibrated activity when measured at the ^{131}I setting. For the ^{131}I solution, the activity reading at the ^{131}I setting is about 2.5 % higher than the calibrated activity, as indicated by the second column. By dividing the values in the first two columns, we obtain a new ratio of the ^{133}Ba and ^{131}I activities that is corrected for the error in the manufacturer's recommended setting for ^{131}I. These values are presented in the third column of Table 1.

Both the average ratio of the ^{133}Ba activity readout value at the ^{131}I setting to the calibrated ^{133}Ba activity and the average ratio of the calibration coefficients obtained from the CRC-12 current measurements are in excellent agreement and indicate that the response of ^{133}Ba in these chambers is 2.94 times higher than that of ^{131}I for an equivalent amount of activity. This striking difference in response ratios demonstrates how differences in chamber construction can have a profound effect on the energy response.

For completeness, the ratios of the readout in the Capintec activity calibrators when measuring the ^{133}Ba ampoules in each instrument using the manufacturer's recommended setting for ^{133}Ba to the calibrated activity are presented in Table 2. The data indicate that the recommended ^{133}Ba setting gives a reading that is an average of 5.2 % high relative to the calibrated activity in the CRC-12 and CRC-15R and 3.7 % for the CRC-35R. The values in Table 2 are not intended to be used as correction factors, but are presented merely to give an indication as to the accuracy in the measurement of ^{133}Ba that can be expected when using the manufacturer's recommended setting. The reason for the observed difference in response between the CRC-12 and CRC-15R and the CRC-35R is not known, but is consistent with

other results published by our laboratory and is within the tolerances quoted by the manufacturer (Capintec 2004).

The correct dial settings for both radionuclides, as measured in each of the activity calibrators used in this study, are given in Table 3. Because of the prevalence of low-energy photon emission and the possible contribution of bremsstrahlung to the response of ^{131}I, users are always encouraged to evaluate the dial settings for these radionuclides for their specific measurement geometry and calibrator using a traceable standard of the actual radionuclide and not rely on surrogates.

The results from this work clearly show that although both ^{133}Ba and ^{131}I both have strong photon emissions at about 360 keV and may initially appear to be well-matched in terms of ^{133}Ba being able to act as a surrogate for ^{131}I, the reality is that substantial errors will result if calibrations for ^{131}I are made using a ^{133}Ba source. Even the smallest difference that we observed, namely 7.5 % for the VIC, is very close to the 10 % error generally accepted for therapeutic applications, and those measurements were made using a calibrated source with a small uncertainty on well-maintained systems. If a source with a larger uncertainty, which would typically be the case for check sources found in most clinics, is used, a 10 % error in administration becomes increasingly likely.

If ^{131}I is used clinically, e very effort should be made to obtain a traceable ^{131}I standard and calibrate the activity calibrator at least once. If a ^{133}Ba source is available, it can make a good long-term monitor of the stability of the ^{131}I calibration if the relative response of the two radionuclides is established when the instrument is first calibrated and routinely measured as part of a quality control system.

5. Conclusion

We have measured the relative responses of standardized solution sources of ^{133}Ba and ^{131}I in several models of activity calibrators from two manufacturers to evaluate the suitability of using ^{133}Ba as a long-lived surrogate for ^{131}I. The results showed that significant errors in the assumed ^{131}I activity, ranging from 7 % to almost 300 % can be realized from this practice, depending on the type of activity calibrator used. Despite the fact that local conditions do not always make it possible or convenient to obtain traceable ^{131}I standards on a regular basis, at least one calibration should be made using such a standard. Barium-133 should not be used as a calibration surrogate for ^{131}I, but it can be used to monitor the stability of a properly performed ^{131}I calibration over time.

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Table 1.Ratios of activity calibrator readout values to NIST-calibrated activity for ^{133}Ba and ^{131}I in three NIST-maintained radionuclide calibrators at the manufacturer's recommended setting for ^{131}I. The third column gives the ratios of the first two columns to provide a ^{133}Ba:^{131}I response ratio that is corrected for the error in the ^{131}I activity introduced from use of the manufacturer's setting. Uncertainties are standard uncertainties and are calculated as described in the text.

	$R(A_{chamber}/A_{NIST})$ ^{133}Ba	$R(A_{chamber}/A_{NIST})$ ^{131}I	$R(^{133}Ba:^{131}I)$
CRC-12, ^{131}I setting	3.01(2)	1.018(5)	2.96(2)
CRC-15R, ^{131}I setting	3.03(2)	1.024(2)	2.96(2)
CRC-35R, ^{131}I setting	2.99(2)	1.029(5)	2.91(2)
Average	3.01(3)	1.024(8)	2.94(4)

Table 2. Ratios of activity calibrator readout values to NIST-calibrated activity for ^{133}Ba in three NIST-maintained radionuclide calibrators at the manufacturer's recommended setting for ^{133}Ba. Uncertainties are standard uncertainties and are calculated as described in the text.

	$R(A_{chamber}/A_{NIST})$ ^{133}Ba
CRC-12, ^{133}Ba setting	1.054(7)
CRC-15R, ^{133}Ba setting	1.051(7)
CRC-35R, ^{133}Ba setting	1.037(8)

Table 3. Experimentally determined dial settings for ^{131}I and ^{133}Ba in the NIST 5 mL ampoule geometry using three NIST-maintained Capintec activity calibrators. The uncertainties are standard uncertainties and are due primarily to the uncertainty in the activity calibration for the respective radionuclide.

Activity Calibrator	DS_{131I}	DS_{133Ba}
CRC-12	156(1)	628(2)
CRC-15R	156(2)	626(2)
CRC-35R	158(2)	618(2)