Standardization of I-124 by three liquid scintillation-based methods


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Abstract

A solution of $^{124}$I was standardized for activity by $4\pi\beta$(LS)-$\gamma$(NaI) live-timed anticoincidence (LTAC) counting, with confirmatory measurements by triple-to-double coincidence ratio (TDCR) and CIEMAT-NIST efficiency tracing (CNET) liquid scintillation counting. The LTAC-based standard was shown to be in agreement (within $k = 1$ uncertainties) with previous measurements at NIST and elsewhere. Calibration settings for radionuclide calibrators were determined and a discrepancy with literature values, partially due to a calibration methodology dependent upon an erroneous setting for $^{18}$F, was identified and explained.

Keywords: Iodine-124; liquid scintillation counting; anticoincidence; Monte Carlo; dose calibrator; positron emission tomography; quantitative imaging; Fluorine-18

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1. Introduction

Since iodine chemistry offers straightforward labeling of monoclonal antibodies, biological receptors, and small-molecule pharmaceuticals, radioiodines have become ubiquitous in nuclear medicine for both therapeutic and imaging applications. In theranostics, positron emission tomography (PET) is increasingly preferred over single photon emission computed tomography (SPECT) due to superior precision (Qaim et al., 2018). In one recent study, PET imaging with $^{124}$I was shown to offer substantial improvements in image quality and quantitation, while requiring 10x smaller activity administrations than $^{123}$I (Beijst et al., 2017). With improving technologies for both production and imaging, $^{124}$I PET has seen increasing use (e.g., Braghirolli et al., 2014).

Quantitative medical imaging, especially when adopted as the basis for patient-specific dosimetry calculations, requires precise nuclear data, and a new evaluation from the Decay Data Evaluation Project (DDEP) meets that need for $^{124}$I (Zimmerman, 2018). Evaluated data are intimately linked with primary activity measurements, as primary methods are both users and progenitors of nuclear decay data. In the case of $^{124}$I, previous primary activity standardizations (Woods et al., 1992; Luca et al., 2016; Sahagia et al., 2016) provide absolute photon emission probabilities for a very complex decay scheme. The National Institute of Standards and Technology (NIST) has previously reported an activity measurement of $^{124}$I by live-timed anticoincidence (LTAC) counting, with emphasis on the complications arising from a complex decay scheme with significant electron capture (EC) contributions (Fitzgerald, 2016). In that work, both multi-dimensional extrapolation and Monte Carlo corrections were necessary to achieve acceptable precision. The LTAC-determined activity was consistent with results of contemporary $4\pi$-$\gamma$ counting.

Here, we revisit the primary standardization of $^{124}$I activity. LTAC is complemented by two additional liquid scintillation (LS)-based methods: triple-to-double coincidence ratio (TDCR)
counting and efficiency tracing with $^3$H. We present the results in the context of the past work at NIST and use ionization chamber (IC) calibration coefficients for context with the standardization of Woods et al. (1992). Finally, we report the findings of ‘dial setting’ determinations on several commercial radionuclide calibrators. The establishment of a National standard in the United States for $^{124}$I activity will provide a new basis for calibrations, supporting improved accuracy and precision in quantitative medical imaging for this increasingly important radionuclide.

2. Methods

2.1. Nuclear data and efficiency calculations

Nuclear data for $^{124}$I were taken from the most recent decay data evaluation project (DDEP) evaluation (Zimmerman, 2018). Electron capture (EC) probabilities were calculated with the LOGFT program (Gove and Martin, 1971) and $\beta^+$ spectrum shape factors, used in the MICELLE2 calculations (*vide infra*), were taken from the measurements of Booij et al. (1971). In GEANT4, the beta spectra were calculated by the G4BetaDecay library, which accounts (in a limited way) for allowed, first-forbidden non-unique transitions, as found in $^{124}$I decay.

The DDEP evaluated data were used to revise the “photo-evaporation” (nuclear deexcitation) and radioactive decay input files for GEANT4 (Agostinelli et al., 2003). Live-timed anticoincidence (LTAC) counting simulations were run with both the original and revised input files, yielding indistinguishable inefficiency curves. The slight differences between the extrapolated intercepts and the true number of Monte Carlo histories were used to calculate correction factors, $f$, to be applied to analogous experimental data. These factors are intended to account for slight intercept biases introduced by differences in the K/L/M capture ratios among EC branches coupled with the low efficiency for LS detection for L and M conversion electrons and x-rays (Funck and
Nylandstedt Larsen, 1983; Fitzgerald, 2016; Fitzgerald et al., 2015), as well as complications from annihilation in flight (Bergeron and Fitzgerald, 2018).

The full decay scheme includes 28 EC transitions and 5 $\beta^+$ transitions, along with scores of accompanying $\gamma$ transitions (Zimmerman, 2018). A simplified decay scheme (Figure 1) was constructed and used to build input files for the 2011 version of the MICELLE2 code (Kossert and Grau Carles, 2010). In the simplified scheme, only one nuclear deexcitation pathway was considered for each level; the major transitions are accounted and are expected to be reasonably representative in terms of LS efficiency. In addition, the $\beta^+_{0,3}-\gamma_{3,1}-\gamma_{1,0}$ cascade was simplified to $\beta^+_{0,3}-\gamma_{1,0}$. Since most of the LS efficiency comes from the $\beta^+$ and the highly converted $\gamma_{3,1}$, we found that this approximation does not affect the calculated LS efficiencies within the output significant figures. Finally, the simplified decay scheme captures nearly all $\beta^+$ decay modes, but neglects approximately 3 % of the EC decays. To calculate LS efficiencies for CNET and TDCR, each branch was run independently in MICELLE2 and the results were combined in a spreadsheet. Renormalization of the branch coefficients was necessary for this combination and the adopted scheme redistributed the “missing” 3 % by applying a common multiplication factor to the nine EC branches, bringing the sum of all $\beta^+$ and EC branch probabilities to one.

Additional MICELLE2 calculations were performed using a Monte Carlo script designed to vary the input files by sampling randomly from gaussian distributions defined by the uncertainties on the evaluated nuclear decay data. In practice, nuclear data uncertainties affected efficiency curves in a similar manner to $kB$ changes; in the uncertainty analysis presented here, a conservative estimate for $kB$ uncertainty was adopted to cover the nuclear data uncertainty.
2.2. Experimental methods

2.2.1. Source preparation

A stock solution containing approximately 37 MBq of $^{124}$I (as NaI) in 2 mL of 0.5 mol L$^{-1}$ NaOH was received from Zevacor Pharma (Richmond, VA)$^2$ and diluted to approximately 25 mL with a 0.1 mol L$^{-1}$ NaOH carrier solution containing LiOH (0.03 mg g$^{-1}$), Na$_2$SO$_3$ (0.03 mg g$^{-1}$), and KI (0.06 mg g$^{-1}$). From this solution, five NIST standard 5 mL flame sealed ampoules were prepared gravimetrically for ionization chamber and/or high-purity germanium (HPGe) measurement. One of the ampoules was opened and diluted gravimetrically to an activity concentration of approximately 50 kBq g$^{-1}$ for preparation of counting sources. Liquid scintillation (LS) sources were prepared with Ultima Gold or Hionic Fluor (PerkinElmer, Waltham, MA, USA). Prior to the addition of $^{124}$I, carrier solution was added to achieve a total aqueous fraction in the cocktails of 0.05. Composition-matched blanks were prepared for background subtraction. For efficiency tracing measurements, quenching was varied across a series of sources via addition of nitromethane; composition-matched $^3$H sources were also prepared from a dilution of SRM 4927F (NIST, 2008). The counting sources were prepared to have nominal activities of 2 kBq when first measured.

2.2.2. Live-timed anticoincidence counting

Four LS sources were prepared in custom glass hemispheres and measured on the NIST live-timed anticoincidence (LTAC) system (Lucas, 1998; Fitzgerald and Schultz, 2008). Efficiency variation was achieved by changing the lower level discriminator threshold for the LS channel.

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$^2$ 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.
Anticoincidence gates were set as described previously by Fitzgerald (2016). Gate 1 was set over the 603 keV ($\gamma_{1,0}$(Te), Figure 1) peak, providing a monitor for LS efficiency of contributions from both EC and $\beta^+$ decays. Gate 2 was set over the 511 keV annihilation peak, monitoring mostly $\beta^+$ decays. Gate 3 covered a range from 1325 keV to 1690 keV, corresponding to higher-energy $\gamma$ rays (and sum peaks) and monitoring mostly EC decays. Contributions from the three gates were weighted as in Equation 1; the weighting coefficients were derived from a least squares fit with the weights and total activity as free parameters to achieve a good linear fit for extrapolation (Baerg, 1981; Fitzgerald et al. 2015; Fitzgerald, 2016),

$$Y_{\text{eff}} = 0.40 Y_1 - 0.01 Y_2 + 0.61 Y_3$$ (1)

Where $Y_n$ is the inefficiency measured with Gate $n$ and $Y_{\text{eff}}$ is the “effective” inefficiency used for extrapolation. Intercepts at $Y_{\text{eff}} = 0$ were adjusted using the correction factor, $f$, indicated by Monte Carlo calculations (Section 2.1) to calculate activities.

2.2.3. Efficiency tracing with $^3$H

Two series of five quenched $^{124}$I sources prepared with Ultima Gold or Hionic Fluor in 20 mL scintillation vials were measured alongside composition-matched $^3$H sources and blanks. Quenching by nitromethane covered a range of $^3$H counting efficiency $\varepsilon_{H-3} = (0.2$ to $0.5)$ counts per decay, corresponding to a range of $^{124}$I counting efficiency $\varepsilon_{I-124} = (0.4$ to $0.6)$ counts per decay. All sources were measured on three occasions, including 10 cycles each, on a Beckman Coulter LS6500 (Beckman Coulter, Fullerton, CA, USA). Sources were also measured for 10 cycles on one occasion on an Aloka AccuFlex LSC-8000 (Hitachi, Tokyo, Japan). Tracing efficiencies were calculated with the MICELLE2 code (Section 2.1) to implement the CIEMAT-
NIST efficiency tracing (CNET) method (Grau Malonda and García-Toraño, 1982; Coursey et al., 1986).

2.2.4. Triple-to-double coincidence ratio counting

Five LS sources were prepared in 20 mL scintillation vials and measured on the NIST triple-to-double coincidence ratio (TDCR) liquid scintillation counter (Zimmerman et al., 2004). Efficiency variation with gray filters achieved a range of triple-to-double coincidence ratios of \( R = 0.82 \) to 0.84 over a range where \( R \) increases with decreasing counting efficiency. Each count was for 600 s (live time), with multiple replicates for each gray filter. Activities were calculated using efficiencies computed with the MICELLE2 code (section 2.1).

2.2.5. Impurities

Photon-emitting impurities were assayed by high-purity germanium (HPGe) \( \gamma \)-ray spectrometry on a detector with a well-characterized efficiency curve (Pibida et al., 2006). Zr-89 was detected with an impurity fraction of \( f_{\text{Zr-89}} = A_{\text{Zr-89}}/A_{\text{I-124}} = 2.0(4) \cdot 10^{-4} \) at the experiment reference time (set to fall in the middle of the measurement campaign), where \( A_i \) is the activity of nuclide \( i \). After several half-lives of decay, \( \text{I-125} \) was detected with \( f_{\text{I-125}} = 1.35(6) \cdot 10^{-3} \) (decay-corrected to the experiment reference time). The \( \text{I-125} \) impurity was also detected with a well-type NaI(Tl) detector and quantified via the sum-peak method (Eldridge and Crowther, 1964), finding \( f_{\text{I-125}} = 1.32(1) \cdot 10^{-3} \).

No other photon-emitting impurities were detected, and LS measurements showed no indications of long-lived impurities contributing spurious counts.

Impurity corrections based on these findings were applied for all methods and the uncertainty on the impurity activity fractions was propagated into the activity assay uncertainties. For TDCR
and CNET, $^{125}$I counting efficiencies were calculated with MICELLE2, while the $^{89}$Zr counting efficiency was estimated as $\varepsilon_{Zr-89} = 0.76$ counts per decay, based on measurements by García-Toraño et al. (2018) in a similar diisopropylnaphthalene-based scintillant. For LTAC, the corrections were $(-1.31 \times f_{I-125})$ and $(-0.54 \times f_{Zr-89})$ as determined by Monte Carlo simulation.

2.2.6. Ionization chambers

Five ampoules were measured in the NIST automated ionization chamber (AutoIC; Fitzgerald, 2010) to establish a calibration factor, $K$. AutoIC measurements of the $^{124}$I ampoules were bracketed by measurements of a $^{226}$Ra reference source (RRS) and an empty sample holder for background subtractions. $K$ is expressed in terms of the ratio, $R$, of measured currents for $^{124}$I and $^{226}$Ra, so that the $^{124}$I activity, $A$, is given according to $K = A/R$. The LTAC study reported in (Fitzgerald, 2016) was used to generate a value for $K$, providing a means of comparing results between experiments.

One ampoule was measured on the Vinten 671 ionization chamber (VIC) (serial number 3-2, Vinten Instruments, Surrey, UK), which is biased to -1500 V and read by a Keithley 6517 A electrometer (Keithley Instruments, Cleveland, OH). Establishing a calibration coefficient for the VIC, $K_{VIC}$ (expressed in terms of pA/MBq), provides a link to other national metrology institutes with related chambers; in this instance, the National Physical Laboratory (NPL, Teddington, UK), as reported in (Woods et al., 1992).

One ampoule was also measured on several commercial reentrant ionization chambers, referred to as radionuclide calibrators (or “dose calibrators”). Responses were recorded at multiple calibration settings and the calibration curve method (Zimmerman and Cessna, 2000) was later used to find the setting that returns the standard activity.
3. Results and Discussion

3.1. LTAC

Figure 2 illustrates the linearity achieved with the adopted gate weighting scheme (Section 2.2.2; Equation 1). The relatively low LS counting efficiency for $^{124}$I results in a long extrapolation. The Monte Carlo simulations show the extrapolation to be robust against the updated nuclear data, changing the expected intercept by less than 0.1%. However, the long extrapolation is sensitive to the selected data ($Y_{\text{eff}}$) range (Table 1), though it appears that the Monte Carlo extrapolations are more sensitive than the experimental data. The final, Monte Carlo-corrected activity was calculated from data in the $Y_{\text{eff}}$ range labeled “3” in Table 1 ($Y_{\text{eff}} = 0.60$ to 0.85), which required the smallest correction factor. A detailed LTAC uncertainty budget is given in Table 2.

3.2. CNET

The CNET measurements were carried out over a period of 8 d and the results were stable for the duration (Figure 3A). In both scintillants, the calculated activities increased with increased quenching (Figure 3B), indicating that the MICELLE2 model using the simplified decay scheme is not perfectly capturing the tracing experiment. The trend is not severe and given the complexity of the decay scheme and the relatively low LS efficiency, the 0.34% relative standard deviation achieved for the quenched series commends the model. Efficiencies were calculated with several values for the Birks parameter, $kB$, and it was observed that the model dependence, measured as the slope of an $A$ vs. quench indicating parameter (QIP) plot, decreased with increasing $kB$ (Figure 3B). This is reflected in the smaller uncertainty bars for higher $kB$ in the CNET series in Figure 4. However, the best agreement with the TDCR results (section 3.3) was achieved near $kB = 0.0075$ cm MeV$^{-1}$, the value suggested by Kossert for Ultima Gold.
(Kossert and Grau Carles, 2010). This canonical value was used to calculate the final CNET activity. A detailed CNET uncertainty budget is available in the supplemental material (Table S1).

3.3. TDCR

For nuclides with EC branches, efficiency variation is particularly important since there is more than one value for the logical sum of doubles efficiency ($\varepsilon_{\text{LSD}}$) for a given $R$ (see, e.g., Broda, 2003; Broda et al., 2007). Our $^{124}$I measurements sampled a portion of the efficiency curve where $\varepsilon_{\text{LSD}}$ decreases with increasing $R$, approaching an inflection point. Figure 5 shows the experimental TDCR data overlaid against the MICELLE2-calculated efficiency curves. The inflection point in the efficiency curve is very sensitive to $kB$, so that it appears that a value between $kB = 0.0060$ cm MeV$^{-1}$ and 0.0075 cm MeV$^{-1}$ best describes the data. The inflection point is also very sensitive to the nuclear data input, so adjusting $kB$ can be considered to compensate for deficiencies in the model resulting from the simplified decay scheme. As for CNET, the canonical value of $kB = 0.0075$ cm MeV$^{-1}$ was used to calculate the final TDCR activity. A detailed TDCR uncertainty budget is available in the supplemental material (Table S2).

3.4. Ionization chambers

The AutoIC calibration factor based on the LTAC results reported in (Fitzgerald, 2016) was applied to the solutions measured herein, returning an activity 0.6 % lower than the activity determined by LTAC, indicating agreement within the $k = 1$ uncertainties. Figure 6 relates the CNET, TDCR, and LTAC activities to the AutoIC activity (a surrogate for the previous LTAC result) and the VIC activity (based on the calibration coefficient reported by Woods et al., 1992).
From our LTAC activity, we determined a VIC calibration coefficient of $K_{VIC} = 10.67(13)$ pA MBq$^{-1}$. Using the normalizing factor, ($n = 1.2$), reported by Woods et al. (1992) with the procedure outlined in the owner’s manual (Vinten, 1984) a value of $K_{VIC, Woods} = 10.69(6)$ pA MBq$^{-1}$ is calculated for 5 mL of solution in a 5 mL ampoule.

Table 3 shows the results of “dial setting” determinations for several Capintec (Ramsey, NJ, USA) radionuclide calibrators. The settings in Table 3 differ from the manufacturer-recommended setting of 570 (Capintec, Inc., 1986); we calculate that the CRC-15R calibrator with a setting of 570 gives a +5 % biased activity. These settings were determined with 5 mL flame sealed ampoules containing 5 mL of solution. Measurements in other geometries, e.g. syringes, will require the use of an alternative setting or a correction factor. Figure 7 places the present determination in context with literature values for several geometries.

Our results are inconsistent with the report by Beattie et al. (2014), who gave a CRC-15R setting of 664 for 10 mL of $^{124}$I solution in a 20 mL liquid scintillation vial. According to our data, a setting of 664 gives a reading that underestimates the $^{124}$I activity in a 5 mL flame sealed ampoule by 8 %. We calculate a difference of 13 % between our $A_{570}$ and $A_{664}$ (where $A$ refers to read activity and the subscript indicates the calibration setting), close to the 14.9 % difference reported by Beattie for the scintillation vial. Some of the difference between our result and Beattie’s is explained by their calibration procedure; Beattie et al. calibrated a HPGe detector for 511 keV annihilation photons using a $^{18}$F source that was calibrated using a NIST-determined dial setting for a syringe containing 3 mL of FDG (Cessna et al., 2008). Since that time, the NIST standard for $^{18}$F activity has been revised (Fitzgerald et al., 2014; Zimmerman et al., 2015), explaining 4.0 % of the present inconsistency with Beattie et al.
Unpublished work at NIST has since revised the setting used by Beattie et al. We found that a setting of 460(9) \((k = 2; \text{with the uncertainty on the dial setting translating to } 1.6\% \text{ uncertainty on the activity reading})\) gives the correct activity reading on a CRC-15R calibrator with a 5 mL syringe containing 3 mL of \(^{18}\text{F}FDG\) in the syringe holder geometry. This revises the 484(5) setting reported by Cessna et al. (2008).

The remaining 4 \% difference between the Beattie et al. (2014) results and ours could be reasonably attributed to geometric effects (i.e., the difference between the ampoule and scintillation vial) and/or difficulties stemming from the HPGe calibration, such as annihilation-in-flight or summing effects (see, e.g., Lépy et al., 2015). Any effect that reduced the HPGe counting efficiency would result in an underestimate of the activity and thus a too-high dial setting. Beattie et al. provide excellent documentation of their methods and provide salient examples of the importance of geometry-specific calibration settings. In the process of preparing this paper, we communicated with Beattie et al. and learned that they have, in fact, revised their calibrator settings for \(^{124}\text{I}\) and \(^{89}\text{Zr}\) in light of the new NIST standard for \(^{18}\text{F}\). The gray arrows in Figure 7 show corrections for the \(^{124}\text{I}\) settings, based on the curves reported by Beattie et al. in their Figure 2B and confirmed by personal communications. We continue to work with Beattie et al. to explain the remaining discrepancy.

Finally, Wooten et al. (2016) also report dose calibrator settings for \(^{124}\text{I}\). They present results for a 2 mL centrifuge tube and a 10 mL syringe. Since we did not consider those geometries and they did not report on measurements in ampoules (or vials, which are more similar to ampoules), our results are difficult to compare. The setting Wooten et al. report for 8 mL in a 10 mL syringe, 733(7), is lower than the 788 setting reported by Beattie et al. for 3 mL in a 5 mL syringe (Figure 7). The Wooten calibrations also relied on HPGe measurements, but their spectrometer was
calibrated with a mixed $\gamma$ source, avoiding the problems with the $^{18}$F standard and possibly resulting in a more accurate calibration.

As both Beattie et al. (2014) and Wooten et al. (2016) admirably demonstrate, ionization chamber measurements of $^{124}$I solutions are very sensitive to geometry and care must be taken to assure accurate administrations and imaging of $^{124}$I-based radiopharmaceuticals. The use of copper filters can reduce sensitivity to volume and geometry effects if filter-specific settings are determined using calibrated sources.

4. Conclusions

Live-timed anticoincidence (LTAC) counting was used to determine the activity of a $^{124}$I solution, with confirmatory measurements by triple-to-double coincidence ratio (TDCR) and CIEMAT-NIST efficiency tracing liquid scintillation counting methods. A new National standard for $^{124}$I was adopted, based on the LTAC measurements and with a combined standard uncertainty of 1.2 % ($k = 1$). Ionization chamber measurements linked the new result with previous measurements at NIST and at the NPL.

Measurements on several commercial radionuclide calibrators showed that a bias of +5 % results from measurements using the manufacturer-recommended calibration setting. As $^{124}$I is increasingly used for medical imaging by positron emission tomography (PET), it is important to assure that accurate activity measurements are possible. Further study of calibrator settings in clinically relevant geometries should be undertaken.

Acknowledgements
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References


Nucleonics 22, 56.


Figure Captions:

**Figure 1** Simplified decay scheme used for LS efficiency calculations. Level numbers correspond to those given in the DDEP evaluation (Zimmerman, 2018). EC branch probabilities are renormalized so that the “missing” decays from neglected cascades are distributed proportionally among the remaining EC branches. For each EC or $\beta^+$, just one $\gamma$ cascade is included. See text for additional details.
Figure 2 Experimental LTAC data (black open symbols), plotted with a linear extrapolation of Monte Carlo-simulated data (dashed red line) over the same inefficiency range, $Y_{\text{eff}}$. The extrapolation intercept at $Y_{\text{eff}} = 0$ gives a number of counts, $N$, that is close to the number of simulation histories, $N_0$, indicating a Monte Carlo correction factor, $f = N_0/N = 1.0007$. The bottom plot shows the relative fit residuals for the experimental (black open symbols) and simulated (red closed symbols). (Color online.)
Figure 3 (A) CNET activities normalized by the combined average CNET activity ($\bar{A}/\bar{\bar{A}}$) plotted over time. The triangles represent Hionic Fluor samples while the circles represent Ultima Gold samples. The open black symbols are from the first run on the Beckman counter, the closed black symbols are from the second run on the Beckman counter, the open red symbols are from the run on the Aloka counter, and the closed gray symbols are from the third run on the Beckman counter. (B) The data from the second run on the Beckman counter, plotted against the tritium counting efficiency (calculated from the QIP). (Color online.)
Figure 4 Dependence on the Birks parameter, $kB$, of activities determined by CNET (triangles) and TDCR (circles). The activities are normalized by the LTAC activity and the uncertainty bars show the LS measurement precision (see Tables S1 and S2).
Figure 5 TDCR efficiency curves calculated with $kB = 0.0060$ cm MeV$^{-1}$ (red dotted trace), $0.0075$ cm MeV$^{-1}$ (black solid trace), and $0.0090$ cm MeV$^{-1}$ (blue dashed trace). Experimental counts (open circles) were normalized by the LTAC activity to give a logical sum of doubles efficiency ($\varepsilon_{LSD}$) at each $R$. (Color online.)
**Figure 6** Comparison of results from the different methods. Uncertainty bars for CNET, TDCR, and LTAC are combined standard uncertainties ($k = 1$). The AutoIC point is based on the calibration factor derived from the LTAC result reported in (Fitzgerald, 2016), with its full combined standard uncertainty ($k = 1$). The VIC* point is based on the calibration coefficient reported in (Woods et al., 1992), with combined ("random and non-random") standard uncertainty ($k = 1$). The VIC point is asterisked because it is based on a calibration from another laboratory (see text).
Figure 7  The ampoule, scintillation vial, 5 mL, and 10 mL syringes are illustrated to show how they would be placed in a Capintec dipper. The Capintec [C], NIST [N], Beattie [B], and Wooten [W] dial settings (DSs) are shown on the number line. The gray arrows illustrate an estimated correction to the Beattie values (using their Figure 2B), assuming a 4 % correction to their calibrated activity to be consistent with the revised NIST standard for $^{18}$F; the open boxes show the estimated corrected settings. The 4 % correction accounts for approximately half of the difference between the NIST DS for a 5 mL ampoule and the Beattie DS for 10 mL of solution in a 20 mL scintillation vial. The uncertainty bars on the NIST setting [N] correspond to expanded ($k = 2$) uncertainties. The uncertainty bars on the Wooten setting [W] correspond to a propagation of a 2 % instrumental uncertainty (Wooten et al., 2016).
Table 1 Experimental LTAC intercepts ($N_0$), Monte Carlo correction factors ($f$), and corrected intercepts ($N_0'$) obtained with data subsets covering different $Y_{eff}$ ranges. $N_0$ values are shown relative to $N_0'$ for range #3.

<table>
<thead>
<tr>
<th>$Y_{min}$</th>
<th>$Y_{max}$</th>
<th>$N_0$</th>
<th>$f$</th>
<th>$N_0'$</th>
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<tr>
<td>1</td>
<td>0.60</td>
<td>0.77</td>
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<td>2</td>
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<tr>
<td>avg</td>
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<tr>
<td>sd / %</td>
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<td>0.74</td>
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Table 2  LTAC uncertainty budget.

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<th>Uncertainty Component</th>
<th>%</th>
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<td><strong>Counting:</strong> Estimated by combining the typical fit uncertainty for a single source in a single measurement run (0.25 %) with the average standard deviation of the mean for a single source on (N = 3) measurement runs (0.15 %)</td>
<td>0.29</td>
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<td><strong>Between Source</strong></td>
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<td><strong>Model uncertainty:</strong> Estimated by combining the standard deviation on the Monte Carlo-corrected activities calculated from linear extrapolations over 5 different efficiency domains (0.49 %) with the standard deviations on intercepts derived from simulations with varied efficiency and quenching parameters (1.0 %)</td>
<td>1.11</td>
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<td><strong>Mass determinations</strong></td>
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<td><strong>Live Time:</strong> Estimated based on previous work</td>
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<td><strong>Background</strong></td>
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<tr>
<td><strong>Impurities:</strong> Estimated by propagating the uncertainty on the (^{125}\text{I}) and (^{89}\text{Zr}) activities and half-lives (Bé et al., 2004; 2011)</td>
<td>(2 \times 10^{-4})</td>
</tr>
<tr>
<td><strong>Half-life:</strong> Propagation of the uncertainty on the (^{124}\text{I}) half-life (4.1760(3) d; Zimmerman, 2018)</td>
<td>0.001</td>
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<tr>
<td>Combined standard uncertainty, (u_c = (\Sigma u_i^2)^{1/2})</td>
<td>1.2</td>
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Table 3 NIST-determined calibrator settings (or dial settings, $DS$) for several radionuclide calibrators with standard combined uncertainty ($k = 1$) resulting from the 1.2 % uncertainty on the standard activity. Using the manufacturer-recommended setting of $DS = 570$ results in a +5 % bias in measured activity ($A$). These settings are for a 5 mL flame sealed ampoule containing 5 mL of solution.

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<th>$DS_{\text{NIST}}$</th>
<th>$A_{570}/A_{\text{LTAC}}$</th>
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<td>CRC-15R</td>
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<tr>
<td>CRC-25PET</td>
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Table S1 CNET uncertainty budget.

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<th>Uncertainty component</th>
<th>u / %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LS measurement precision:</strong> calculated by combining the average standard deviation (0.14 %) on 10 replicate determinations on 10 sources (i.e., within source variance) with the average standard deviation (0.34 %) on the determined activities for 5 sources with each scintillant (i.e., between source variance), the standard deviation (0.10 %) on 3 repeat determinations on the same counter (i.e., run-to-run variance), the standard deviation (0.11 %) on the average determinations with 2 different LS counters (3 determinations on the Beckman, 1 determination on the Aloka; i.e., counter-to-counter variance), and the standard deviation (0.07 %) on the average determination with each of 2 scintillants (i.e., between scintillant variance).</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Background:</strong> propagation of the standard deviation of the mean of multiple background determinations within each counting run</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Quench indicating parameter measurements:</strong> wholly embodied in LS measurement precision</td>
<td></td>
</tr>
<tr>
<td><strong>H-3 activity:</strong> propagation of the uncertainty on the certified massic activity of SRM 4927 F (0.36 %; 1998 calibration by gas counting) (NIST, 2008)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Decay correction:</strong> propagation of the uncertainty on the $^{124}$I half-life (4.1760(3) d; Zimmerman, 2018)</td>
<td>$8 \times 10^{-4}$</td>
</tr>
<tr>
<td><strong>H-3 decay correction:</strong> propagation of the uncertainty on the $^{3}$H half-life (12.312(25) a; Bé et al., 2006)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Model uncertainty:</strong> estimated uncertainty due to $kB$ (= 0.0075(15) cm MeV$^{-1}$) combined with the typical standard error of the polynomial used to fit the MICElle2 efficiency curves</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Impurities:</strong> propagation of the uncertainties on the $^{89}$Zr and $^{125}$I activities, half-lives (Bé et al., 2004; 2011), and LS counting efficiencies</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Weighing uncertainty</strong></td>
<td>0.05</td>
</tr>
</tbody>
</table>

Combined standard uncertainty, $u_c = (\sum u_i^2)^{1/2}$ | 0.79  |
Table S2  TDCR uncertainty budget.

<table>
<thead>
<tr>
<th>Uncertainty component</th>
<th>( u / % )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LS measurement precision:</strong> calculated by combining the typical standard deviation (0.10 %) on replicate determinations (( N = 5 ) to 75) for a single source with a single gray filter (i.e., within source variance) with the standard deviation (0.32 %) on the determined activities for 6 sources with the same gray filter (i.e., between source variance), and the typical standard deviation on the activities determined with different gray filters (0.10 %)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Background:</strong> propagation of the standard deviation of the mean on multiple background determinations</td>
<td>( 2 \times 10^{-4} )</td>
</tr>
<tr>
<td><strong>Decay correction:</strong> propagation of the uncertainty on the (^{124}\text{I}) half-life (4.1760(3) d; Zimmerman, 2018)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Model uncertainty:</strong> estimated uncertainty due to ( k_B ) (= 0.0075(15) cm MeV(^{-1})); model uncertainty is partially embodied in the LS measurement precision</td>
<td>1.56</td>
</tr>
<tr>
<td><strong>Impurities:</strong> propagation of the uncertainties on the (^{89}\text{Zr}) and (^{125}\text{I}) activities, half-lives (Bé et al., 2004; 2011), and LS counting efficiencies</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Weighing uncertainty</strong></td>
<td>0.05</td>
</tr>
</tbody>
</table>

Combined standard uncertainty, \( u_c = (\sum u_i^2)^{1/2} \) | 1.6          |